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APPLICABILITY OF EXPERIMENTAL RESULTS TO THE SHOCK PROBLEM IN MAN

CHAIRMAN'S ADDRESS

CARL J. WIGGERS, M.D., Sc.D.

CLEVELAND

It has become traditional in this section for the chairman to offer some sort of overture to our proceedings. Since the symposium today stresses the services that physiology has rendered to medicine, and since these contributions have accrued largely through animal experimentation, I have chosen to discuss the applicability of results so gained to the shock problem in man.

The statement is frequently made that experiments rarely, if ever, reduplicate diseases in man, and that therefore only those deductions are applicable which are derived from experiments which simulate clinical conditions, and only those interpretations are valid which agree with clinical observations. In the experimental study of shock, experimenters have been criticized and have criticized one another in the use of unnatural and uncomparable methods. To be frank, too many laboratory investigators have studied shock who have never seen a case clinically and hence are perhaps unable to judge the similarity of conditions. It is likewise true, however, that surgeons having a large clinical experience with shock have sometimes attempted types of experiments for the performance or interpretation of which they lacked the requisite laboratory training. I have candidly analyzed these problems in a recent address,[1] in which I pointed out the rapid improvement that is being made in the situation and the pathways that must be trod to improve conditions still more.

A primary requisite in the experimental study of shock is to have criteria which indicate that a state has been produced which is similar to that observed in traumatic, surgical and toxemic shock of man. Difficulties arise because some of the best signs and symptoms of human shock are not exhibited by animals. Pallor of the skin and generalized sweating are absent in dogs, for obvious reasons. The drawn countenance, an anxious facial expression, apathy, muscular weakness are obscured in dogs by the necessary anesthesia. For this reason the common cardiovascular signs—fall in arterial pressure, cardiac acceleration, small thready pulse and pallor of mucous membranes—have been generally used as criteria of shock in animals. However, these signs are observed also in various hypotensive states not generally classified as shock because they do not end fatally if untreated and are variously called primary shock, syncope, collapse or vasogenic shock.

The best criterion of shock in animals and man so far suggested is the coexistence of a reduced cardiac output and hypotension. Other signs, such as hemoconcentration and reduction in blood volume, are frequently demonstrable and may even precede the decline in cardiac output or arterial pressures. But a state of shock, in the age long usage of the term, cannot be said to have begun until these dynamic criteria are satisfied. I emphasize this point despite a strong trend of opinion that shock can be detected through studies of the blood before arterial pressure falls. Certainly not every human subject or animal who shows hemoconcentration or even a reduced circulating volume develops an irreversible state of circulatory failure which ends fatally if untreated. The events which lead to an irreversible state of circulatory failure are not set into operation until the reduction of effective blood volume can no longer be compensated by mobilization of blood from various reservoirs, such as the spleen, liver, skin and perhaps the lungs. Dominated by modern thinking, many clinical diagnoses of incipient shock are being made on the basis of blood studies, and beneficial effects are claimed for various forms of therapy, when it was never clear that shock would have eventuated without such remedies. I would not decry, but on the contrary urge, the prompt employment of agents which could do no harm even if shock did not develop. I merely desire to emphasize that we should not claim to have rescued patients from certain death or to have established the value of remedies or procedures by such criteria alone. Similarly, experimenters who have merely demonstrated that certain agents cause some reduction in blood volume or hemoconcentration may not infer that an incipient stage of shock existed.

PROCEDURES USED

On the basis of the dynamic criteria fall in blood pressure and reduced cardiac output, a large number of procedures applied to animals can produce a state of shock, but they do not invariably do so. As a matter of expediency they have been arranged in three groups for discussion:

GROUP 1.—Hemorrhage; crushing of muscles, bones or testes; burns; intestinal obstruction; exposure of intestine and traction on mesentery; irradiation of abdomen; adrenalectomy; introduction of foreign organic material into the peritoneal cavity; prolonged anesthesia.

GROUP 2.—Prolonged hyperthermia, prolonged freezing or immersion in ice water; introduction of ice or ice water in the abdominal cavity, rectum or intestinal loops; cauterization or traumatism of intestine or liver; massage of the stomach, and so on.

GROUP 3.—Injections of fat emulsions; excessive pulmonary ventilation; compression of the inferior vena cava; pericardial effusions; occlusion of pulmonary arteries; prolonged compression of the aorta; prolonged stimulation of afferent nerves;

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Read before the Section on Pathology and Physiology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 4, 1941.

1. Wiggers, C. J.: Pathways of Medical Progress, Science **93**:1 (Jan. 12) 1940.

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prolonged injection of epinephrine; intravenous injections of (*a*) muscle and tissue extracts, (*b*) blood and serum from animals in shock, (*c*) peptones, histamine, adenylic acid, potassium, and so on; release or exclusion of blood from damaged regions.

Group 1 includes a variety of procedures which are reasonably comparable to those that nature employs. It has been questioned whether hemorrhage alone can cause shock. Hence it seems important that the subject be studied further in different laboratories. Werle and Cosby,[2] who recently did so in our laboratory, were able to confirm Blalock's conclusion that it can do so. However, our hopes that hemorrhage might constitute a procedure that is sure and can be standardized have not been realized so far. Hemorrhage per se may of course reduce cardiac output and lower arterial pressure, and an animal may die through respiratory failure. But if blood is withdrawn according to a proper time-volume scale so that acute respiratory failure does not supervene or is prevented by various experimental means, hemorrhage eventuates in a state of circulatory failure which is not permanently alleviated by restoration of all the withdrawn blood (heparinized). It is true, as Moon correctly observed, that the viscera are generally pale when dogs die of hemorrhage alone; but when they die after restoration of the blood following a prolonged period of hypotension, all the pathologic signs—capillary congestion, edema, effusions, petechial hemorrhages and so on—are found in the viscera, notably the intestine. The only exception is that the spleen is frequently engorged, not shrunken and hard. However, a perusal of the literature reveals considerable difference of opinion among investigators regarding the state of this organ after death from shock.

That the other procedures listed in group 1 can produce shock is rarely disputed. Moon's procedure of placing macerated muscle, liver, bile and so on in the peritoneal cavity unquestionably produces a state of shock resembling that which follows peritonitis, maceration or necrotization of abdominal tissues, toxemia and the like, regardless of whether one agrees or not that it produces shock by the same mechanisms as in traumatic shock. Whether anesthesia causes death otherwise than through primary cardiac or respiratory failure may be questioned; but many believe that a true state of shock can be produced by prolonged anesthesia alone.

I feel confident that barbital, properly used as an animal anesthetic, is not such an agent, provided anesthetizing doses are biologically determined for each animal. The blood pressure is maintained and, if kept warm, the dog recovers without abnormalities of action or habit. It is true that Seevers and Tatum[3] reported some congestion of viscera, especially of the brain, but it must be stressed that this occurred after chronic barbiturate poisoning and not after a single anesthetic dose. Morever, death was not due to shock but usually to convulsions. Our experience extending over a period of twelve years rather coincides with that of Seeley, Essex and Mann [4] that barbiturates seem to offer some protection against induction of shock. The chief drawback is the slight depressant effect on the respiratory center or pathways so that cessation of respiration, followed by an abrupt further decline of blood pressure, readily occurs when arterial pressures have fallen to critically low levels. This must be prevented by temporary mild artificial respiration or by other experiments, should it occur. Such death from respiratory failure must be clearly distinguished from that due to shock per se.

Group 2 includes a list of experimental procedures which, except possibly for prolonged freezing or hyperthermia, are rarely, if ever, provocative of shock in man. All represent rather drastic methods apparently employed in the hopes of inducing shock with greater certainty than by measures listed in the first group.

Group 3 contains a great assortment of procedures which bear no semblance to causes of human shock. I shall consider some of these in greater detail, because the purpose of such experiments has often been misunderstood or misrepresented. It is the task of laboratory investigators not merely to reproduce shock by methods that nature uses but to test the validity of clues so gained by experiments of quite a different type. Indeed, an investigator's ingenuity in designing such experiments is often a criterion of eminence in research. We may profitably review a few contributions to the shock problem made by such older studies, if only to reassure ourselves that the dogs so sacrificed have not died in vain and that humane use of stray animals remains necessary for the solution of the shock problem.

Fat Embolism.—Since some of the clinical symptoms of fat embolism resemble those of shock and since it was put forward again by an eminent physiologist [5] as a cause of traumatic shock, the question required reinvestigation whether this could produce the essential circulatory changes of shock. It was found that venous injections of fat emulsions may under certain circumstances cause a fall in arterial pressure, generally through pulmonary embolism. But when this happens pulmonary, arterial and venous pressures rise significantly; they do not fall as in shock (Bissell,[6] Simonds,[7] Wiggers [8]).

Excessive Pulmonary Ventilation.—This constitutes one of the strikingly unnatural methods for producing shock; nevertheless, on the basis of such experiments Henderson [9] in 1908 formulated the idea which remains basic to our current conception of shock. In 1910, when the concept of a venopressor mechanism was more clearly formulated, he stated that "venous pressure is, so to speak, the fulcrum of the circulation . . . shock, as surgeons use the word, is due to a failure of the fulcrum. Because of the diminished venous supply, the heart is not adequately distended and filled during diastole. Hence the picture of a 'failing heart' revealed by the pulse. For the same reason, arterial pressure ultimately sinks in spite of an intense activity (not because of failure) in the vasomotor nervous system, and in spite of constriction (not because of relaxation) of the arterioles." What is generally added to such a description of the basic sequence of events today? We could wish, it is true, that Henderson's numerous papers had contained more experimental evidence and less rhetoric. Their careful rereading fails to reveal that decrease in venous return, venous pressure or ven-

2. Werle, J. M., and Cosby, R. S.: Initiation of Shock Through Loss of Blood or Plasma, Am. J. Physiol. **134:** 299, 1941.

3. Seevers, M. H., and Tatum, A. L.: Chronic Experimental Barbital Poisoning, J. Pharmacol. & Exper. Therap. **42:** 217 (June) 1931.

4. Seeley, S. F.; Essex, H. E., and Mann, F. C.: Comparative Studies on Traumatic Shock Under Ether and Sodium Amytal Anesthesia: Experimental Research, Ann. Surg. **104:** 332 (Sept.) 1936.

5. Porter, W. T.: Traumatic Shock, Harvey Lectures **13–14:** 21, 1917; Fat Embolism, a Cause of Shock, Boston M. & Surg. J. **176:** 248 (Feb. 15) 1917.

6. Bissell, W. W.: Pulmonary Fat Embolism: A Frequent Cause of Postoperative Surgical Shock, Surg., Gynec. & Obst. **25:** 8 (July) 1917.

7. Simonds, J. P.: A Study of Low Blood Pressures Associated with Peptone Shock and Experimental Fat Embolism, J. A. M. A. **69:** 883 (Sept. 15) 1917.

8. Wiggers, C. J.: Fat Emboli and Shock, Proc. Soc. Exper. Biol. & Med. **15:** 34, 1917.

9. Henderson, Yandell: Acapnia and Shock, Am. J. Physiol. **21:** 126 (Feb.) 1908; Acapnia and Shock: VII. Failure of the Circulation, ibid. **27:** 152 (Nov.) 1910.

tricular filling were actually demonstrated as a result of any procedure other than excessive pulmonary ventilation. Such evidence was subsequently supplied by my demonstrations [10] that effective venous pressure falls after hemorrhage, infliction of trauma and intestinal manipulation and by the demonstrations of Blalock and his associates [11] that cardiac output decreases during shock produced by hemorrhage, trauma, burns and intestinal manipulation. Thus the concept of reduced venous return and diminished cardiac output clearly formulated by Henderson became a demonstrated fact in various types of shock.

Venous Congestion.—No experimentalist was so simple that he believed compression of the vena cava, pericardial effusions or pulmonary embolism could be natural causes of shock. The procedures were used to test the possibility that venous congestion combined with diminished cardiac output could produce changes which led to an irreversible circulatory failure after removal of the offending agent. It was found [12] that compression of the inferior vena cava or hepatic vein produces a packing of blood in capillaries of the liver, intestine and spleen, together with profuse secretion of fluid by serous and mucous surfaces of abdominal viscera. The fluid actually lost from the blood stream combined with that which remained immobile in dilated capillaries was considered responsible for the reduced venous return in these cases. Similar effects resulted from prolonged pericardial compression (Cannon [13]) if blood pressure was maintained at critically low levels.

These observations fitted in with evidence which subsequently accumulated in man and animals that the blood is concentrated during shock and that its circulating volume is diminished. The experiments mentioned were precursors also to subsequent discoveries that, after trauma, sufficient blood or plasma could be drained into tissues to initiate the progressive circulatory failure.[14] It remained, however, to account for the fluid which apparently disappears in types of shock in which such loss is not an obvious feature. To this end, other types of experiments needed to be devised.

Retardation of Capillary Flow from the Arterial Side.—This was produced by various experiments. The aorta was compressed for a long period and then released; prolonged constriction of peripheral vessels was induced by epinephrine and, reflexly, by stimulation of nerves. The results obtained were interpreted as favoring the conclusion that prolonged impairment of peripheral flow by the first two of these methods leads to anoxia or asphyxia and this to capillary dilatation and increased permeability. This was consonant with the constricted state of cutaneous vessels found in clinical forms of shock and with supplementary experimental evidence that the peripheral vessels are constricted early in shock. Hence the interpretation was launched that arteriolar constriction by creating a state of tissue anoxia represents the initiating factor in shock. I [15] have recently reviewed the evidence and given reasons why it is not convincing to me. Briefly they are as follows:

1. A review of the literature reveals four good investigations indicating that peripheral vessels are initially constricted, but also four which indicate that peripheral resistance is reduced.

2. It has not been demonstrated that the total resistance to flow from the aorta is decreased in early stages of shock.

3. Experimental and clinical forms of hypertension in which total peripheral resistance is greatly increased does not eventuate in shock, and no one has succeeded in inducing shock by prolonged vasoconstriction produced by stimulating afferent nerves.

4. Large, unnatural doses of epinephrine which are assumed to cause shock by vasoconstriction have deleterious effects on the heart and pulmonary circulation.

Constriction of surface vessels, as that of the spleen, probably constitutes a compensatory mechanism for placing larger volumes in circulation through the viscera rather than a mechanism for initiation of shock. Admitting a degree of constriction in skin and muscles to the point of serious anoxia, it is curious that somatic structures show so few pathologic changes. Pertinent also are the impressions which Dr. Werle and I have gained that permitting experimental animals to cool seems to delay rather than to favor the onset of shock.[16]

Nevertheless, many investigators continue to stress the importance of vasoconstriction and consequent anoxia either as an initiating or as a sustaining factor in shock. In any event, we must thank original experiments which superficially had little semblance to natural shock for a concept that can now be submitted to further study.

The Search for Toxic Factors.—The possibility that toxic agents might be responsible for capillary stagnation, reduction in blood volume, decrease in venous return, and the like required many experimental studies. Various substances, including blood from shocked animals, fluid from traumatized regions, or fluid accumulating during intestinal obstruction, and so on were injected into normal animals. Clever autotransfusion and cross circulation experiments were devised. All of these yielded variable results in the hands of different investigators, which are still difficult to evaluate and harmonize. However, the bulk of evidence indicated that extracts or autolysates of most organs of the body, including breakdown of red cells, causes a pronounced fall in blood pressure. Admittedly, such experiments are far from crucial evidence that similar toxic agents

10. Wiggers, C. J.: The Initial and Progressive Stages of Circulatory Failure in Abdominal Shock, Am. J. Physiol. **45:** 485 (March) 1918; Shock and Circulatory Failure Following Trauma, ibid. **46:** 314 (June) 1918.

11. Blalock, Alfred: The Regulation of Circulation: V. The Effect of Anemia and Hemorrhage on the Cardiac Output of Dogs, Am. J. Physiol. **80:** 157 (March) 1927; Mechanism and Treatment of Experimental Shock; Shock Following Hemorrhage, Arch. Surg. **15:** 762 (Nov.) 1927. Butler, Virginia; Beard, J. W., and Blalock, Alfred: Experimental Shock: Study of Alterations in Volume of Blood and in Water Content of Blood and of Muscle That are Produced by Histamine, Arch. Surg. **23:** 848-854 (Nov.) 1931.

12. Janeway, H. H., and Jackson, H. C.: The Distribution of Blood in Shock, Proc. Soc. Exper. Biol. & Med. **12:** 193, 1915. Morison, R. A., and Hooker, D. R.: Vascular Tone and the Distribution of the Blood in Surgical Shock, Am. J. Physiol. **37:** 86 (April) 1915. Erlanger, J.; Gasser, H. S., and Meek, W. J.: Studies in Secondary Traumatic Shock: IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development; VI. Statistical Study of the Treatment of Measured Trauma with Solutions of Gum Acacia and Crystalloids, ibid. **50:** 31, 119 (Oct.) 1919. Hepler, O. E., and Simonds, J. P.: Mechanism of Shock: Effects of Intravenous Injection of Salt Solution in Collapse Induced by Mechanical Impounding of Blood in Splanchnic Region in Normal and in Hyperthyroid Dogs, Arch. Path. **25:** 149 (Feb.) 1938.

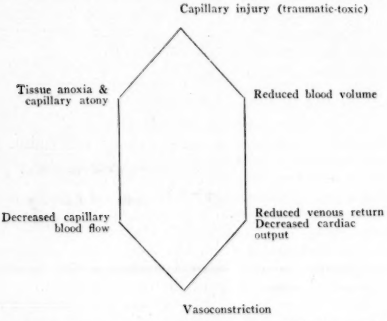
13. Cannon, W. B., and Cattell, McKim: Experimental Traumatic Shock: Critical Level in Falling Blood Pressure, Arch. Surg. **4:** 300 (March) 1922.

14. Mann, F. C.: Studies on Experimental Surgical Shock, Am. J. Physiol. **47** 231 (Nov.) 1918. Smith, M. I.: Studies on Experimental Shock with Especial Reference to Its Treatment, J. Pharmacol. & Exper. Therap. **32:** 465 (April) 1928. Parsons, E., and Phemister, D. B.: Hemorrhage and "Shock" in Traumatized Limbs; Experimental Study, Surg., Gynec. & Obst. **51:** 196 (Aug.) 1930. Blalock, Alfred: Experimental Shock: Cause of Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20:** 959 (June) 1930; Experimental Shock: Probable Cause for Reduction in Blood Pressure Following Mild Trauma to Extremity, ibid. **22:** 598 (April) 1931; Shock: Further Studies with Particular Reference to Effects of Hemorrhage, ibid. **29:** 837 (Nov.) 1934.

15. Wiggers, C. J.: The Mechanism of Peripheral Circulatory Failure, Ann. Int. Med. **15:** 178 (Aug.) 1941.

16. I was gladdened a few days ago when Blalock (George Brown Memorial Lecture, American Heart Association, Cleveland, May 31) announced that he likewise had been forced to consider such an unorthodox possibility. Blalock added, what had not occurred to me, that settlement of this possibility is of greatest immediate importance in the management of patients in shock.

are absorbed and produce shock. Many specific toxic substances have been accused of guilt, but, as a result of experiments by such eminent investigators as Bayliss, Cannon, Dale, Laidlow, Lewis and Richards, histamine came to be suspected quite generally as the guilty substance. It not merely causes a decline of arterial and venous pressures but also acts as a capillary poison; it increases lymph flow, produces marked tissue edema and leads to hemoconcentration. The postmortem appearance of tissues is also similar to that which occurs in shock due to natural agents. Many arguments developed out of additional experimental work seemed to exonerate histamine as a cause of shock following trauma. It was reported that, unlike true shock, (1) arterial pressure declines before cardiac output, (2) the bleeding volume required to produce death after histamine is much greater than after true shock, (3) the distribution of the reduced blood flow is different in histamine shock and traumatic shock, (4) the water concentration of tissues is also different and (5) traumatized muscles are capable of yielding comparatively little histamine. Finally, opinions differ as to whether or not the histamine content of blood increases. To me,



many of these arguments are not convincing. The chance is great that some of the differences mentioned are fortuitous rather than of fundamental importance. It is certainly too early to abandon the concept that a toxic agent is concerned. If one exists, its isolation would certainly open large fields for exploration, much as the discovery of insulin did in the study of carbohydrate metabolism. The greatest impediment in the investigation of shock today is the lack of any quantitative or even any certain method for its production. Lacking this, much good information should still be obtainable from quantitative studies of "histamine shock," regardless of whether or not histamine ultimately proves to be a factor in other forms of shock.

Failure as yet to identify a toxic factor does not preclude its existence. The possibility is great that more than one substance is concerned in different types of shock; it is likewise not impossible that an interaction or activation of some substance may be required, as seems to be the case of renin. Finally, participation of endocrine glands may be concerned, which would account for the terminal circulatory failure following Addison's disease or adrenalectomy.

This very incomplete analysis of the purpose of many experimental studies should suffice to remove the charge that experimenters have unwittingly chosen unnatural experimental methods for producing shock. On the contrary, such experimental work has given rise to the conception that shock is induced by a vicious cycle of events as schematically indicated in the illustration.

The differences of opinion which generally exist concern chiefly the question whether the cycle starts at the first, second or fourth position—in other words, Which is the initiating and which are the sustaining factors? Such a crystallization of ideas regarding the mechanisms of shock may not prove correct or complete, but it has the merit that it offers something definite to support, revise or disprove by additional experiments.

Finally, despite the demonstration that shock can be produced in animals by procedures which resemble catastrophes concerned in man, experimenters will probably agree that none of these procedures do so without fail. Clinical observers are also inclined to postulate a refractoriness or insensitivity of patients to shock-producing agents. Perhaps these refractory cases are the more instructive. It is not so strange that shock can be produced by catastrophes short of being immediately fatal; it is, on the contrary, remarkable that, so often, the body has sufficient resistance to withstand them. Unquestionably, greater emphasis on factors which prevent the development of irreversible shock rather than on those responsible for its development may supply a valuable key to our understanding of the problem. A careful study of the literature on shock and some experimental experience convince me that shock begins with a decrease in effective circulatory volume, as generally believed, but that the operation of some precipitating factor—or failure of some compensating mechanism—is required to cause the irreversible state of circulatory failure to which the term shock ought perhaps be restricted.

If such a precipitating factor exists it is probably associated either (*a*) with creation of an irreversible damage to capillaries so that they no longer hold fluid or (*b*) with inability of compensating mechanisms to maintain an arterial pressure sufficient to supply vital tissues with blood. Both may be concerned. If the former is involved, the moment when irreversible capillary damage appears may depend on the extent to which humoral agents, e. g. hormones of the adrenal cortex, continue to be supplied. This is indeed the concept first suggested by Swingle and his associates [17] and subsequently developed by Selye [18] in the "defense mechanism" theory of adrenal cortical function.

It is, however, also conceivable and without prejudice to the view that capillary stagnation and loss of fluid represent initiating and sustaining factors in the evolution of shock, that the eventual determinant of circulatory recovery or failure does not lie in the capillaries at all. Thus, irreversible circulatory failure often does not eventuate after toxic doses of histamine, despite a demonstrable early increase in capillary permeability and presence of generalized visceral edema.[19] When death occurs, some other precipitating agent seems to be introduced.

Such determinants of irreversible failure may concern (1) failure of moderator reflexes which normally act

17. Swingle, W. W., and Parkins, W. M.: Comparative Study of the Effect of Trauma on Healthy Vigorous Dogs With and Without Adrenal Glands, Am. J. Physiol. **111:** 426 (March) 1935; Study of the Circulatory Failure and Shock Following Trauma to the Healthy, Vigorous Adrenalectomized Dog, ibid. **124:** 22 (Oct.) 1938; Effect of Priming Doses of Desoxycorticosterone Acetate in Preventing Circulatory Failure and Shock in the Adrenalectomized Dog, ibid. **132:** 249 (Feb.) 1941.

18. Selye, Hans; Dosne, Christianne; Bassett, Lucy, and Whittaker, Joan: On Therapeutic Value of Adrenal Cortical Hormones in Traumatic Shock and Allied Conditions, Canad. M. A. J. **43:** 1 (July) 1940.

19. McCarrell, J. D., and Drinker, C. K.: Cervical Lymph Production During Histamine Shock in the Dog, Am. J. Physiol. **133:** 64 (May) 1941.

to stabilize blood pressures, (2) failure of mechanisms which mobilize blood from various blood depots into the general circulation, (3) failure of processes which aid venous return or (4) those which adapt the size of the large arteries to the cardiac output and blood volume.

Finally, it is not impossible that the myocardium becomes impaired as a result of prolonged hypotension with the result that the heart fails to eject as much blood as it should with venous pressures that do exist. In investigations in progress, Dr. Werle and I have noticed a tendency for a premortal recovery in venous pressure which seems related to insufficient pumping action of the ventricles. In other experiments, a marked slowing of the heart, not attributable to vagus action, has the same effect on venous pressures.

My better judgment warns me, however, that my discourse should be terminated before I am tempted to reassign the real failure of the circulation to the heart, where it was placed up to fifty years ago.

THE BARBITURATES AND THE THIOBARBITURATES

SOME DIFFERENCES IN THEIR ACTIONS WHEN ADMINISTERED TO HUMAN BEINGS AND TO EXPERIMENTAL ANIMALS

CHAIRMAN'S ADDRESS

CHARLES M. GRUBER, M.D.
PHILADELPHIA

From the standpoint of chemistry, the derivatives of barbituric acid are divided into two main groups, those with an oxygen in the number 2 position (as shown in the table) known as the barbiturates, and those in which this oxygen has been replaced by sulfur, the thiobarbiturates. In the compounds available today the substitution of sulfur for oxygen has increased their instability and shortened their actions.

Fitch and Tatum [1] were the first to recognize the possibility of classifying the barbiturates according to their durations of action. These drugs may be regarded as long, intermediate, short and ultrashort acting barbiturates. Except for this difference in duration of action and other minor differences in quality of action, the barbiturates as a whole behave strikingly alike. The differences in duration of action can be most accurately determined when these drugs are injected intravenously to eliminate variations in rate of absorption which occurs when they are given orally. Werner, Pratt and Tatum [2] have emphasized this factor as being especially important in experimental animals.

In the human subject, as in the experimental animal, a barbiturate listed in the short acting group may behave as one of longer action because of any one or all of the following factors: (1) slow rate of either excretion or destruction of the preparation administered, (2) slowed absorption of the drug yet adequate absorption to produce its effect, (3) a large dose having been administered, (4) increased susceptibility of the patient to the drug, (5) the use of fractional dosages.

In considering the probable duration of action of any of the barbiturates, the approximate functional capacities of both the kidneys and the liver should be known. Those drugs which are excreted mainly in the urine [3] (barbital, phenobarbital and their sodium salts) must be given cautiously in cases of nephritis, and most of the remaining barbiturates with the possible exception of pentothal, which are mainly destroyed by the liver, should be carefully prescribed in cases of hepatitis and in other forms of liver damage.[4] In these the rate of absorption is an all important factor.

The amount of the drug administered definitely influences its duration of action in the average patient. If the dose is smaller than the customary therapeutic dose the resulting action will be shorter, and if it is larger than the usual dose the action will be longer than that ordinarily observed. This can be seen in patients who have taken amounts larger than the average therapeutic doses for suicidal purposes.[5]

Peculiarly enough, the barbiturates do not cause depression of the central nervous system in all patients. Indeed, some react to therapeutic doses by excitement, delirium and even hallucinations. I might add that persons have been sent to mental observation wards because of the physician's unfamiliarity with the peculiar responses of some patients to these drugs. Other patients are hypersensitive to these chemicals and even therapeutic doses will cause profound sedation.

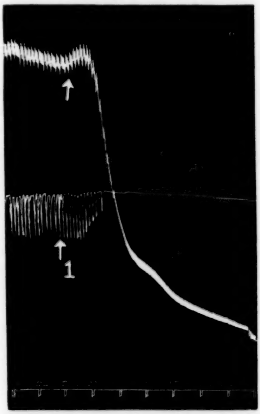


Fig. 1.—Dog weighing 10 Kg. Ether anesthesia. Top record, blood pressure with a mercury manometer; bottom line, the time in intervals of fifteen seconds and zero blood pressure. Middle record that of respiration. Down stroke in the respiratory record is inspiration. At 1, 10 mg. of pentothal per kilogram was injected intravenously in one minute. Respiration stopped in expiration, the heart continued to beat and the animal died a respiratory death.

The administration of the thiobarbiturates by the fractional dose method should receive special attention here, since they differ from most of the barbiturates. Although the initial dose of a series of pentothal sodium (thiopentobarbital) may cause anesthesia in experimental animals varying from seven to twenty minutes, Veal and Reynolds [6] have shown that, as the subsequent fractional doses are administered, the resulting anesthe-

From the Department of Pharmacology, Jefferson Medical College.
Read before the Section on Pharmacology and Therapeutics at the Ninety-Second Annual Session of the American Medical Association, June 5, 1941.

1. Fitch, R. H., and Tatum, A. L.: Duration of Action of the Barbituric Acid Hypnotics as a Basis of Classification, J. Pharmacol. & Exper. Therap. **44:** 325 (March) 1932.

2. Werner, H. W.; Pratt, T. W., and Tatum, A. L.: A Comparative Study of Several Ultrashort-Acting Barbiturates, Nembutal and Tribromethanol, J. Pharmacol. & Exper. Therap. **60:** 189 (June) 1937.

3. Hirschfelder, A. D., and Haury, V. G.: Effect of Nephrectomy on Duration of Action of Barbitals, Proc. Soc. Exper. Biol. & Med. **30:** 1059 (May) 1933.

4. Pratt, T. W.: A Comparison of the Action of Pentothal (Nembutal) and Sodium Barbital in Rabbits as Related to the Detoxicating Power of the Liver, J. Pharmacol. & Exper. Therap. **48:** 285 (July) 1933. Koppanyi, Theodore; Dille, J. M., and Linegar, C. R.: The Effect of Prolonged Chloroform Anesthesia on the Duration of Action of Barbiturates, ibid. **58:** 119 (Oct.) 1936. Cameron, G. R., and de Saram, G. S. W.: The Effect of Liver Damage on the Action of Some Barbiturates, J. Path. & Bact. **48:** 49 (Jan.) 1939. Kohn, Richard, and Grimes, Clyde: Studies on the Detoxification of Sodium Pentobarbital Under Various Conditions, J. Pharmacol. & Exper. Therap. **63:** 18, (May) 1938.

5. Bleckwenn, W. J., and Masten, M. G.: The Antidotal Treatment of Barbiturate Intoxication, J. A. M. A. **111:** 504 (Aug.) 1938.

6. Veal, J. R., and Reynolds, Chapman: The Cumulative Effects of Pentothal Sodium, South. M. J. **31:** 649 (June) 1938.

sia is increased in duration, lasting from forty to fifty minutes, thus making it possible to classify them among the short acting rather than with the ultrashort acting barbiturates.

The value of the barbiturates in therapeutics lies in the fact that their main site of action is the brain. In small effective doses they serve as hypnotic agents and in larger doses they may cause anesthesia.

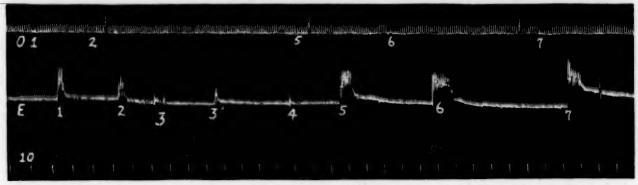


Fig. 2.—Two albino rats were used. These records were made by attaching levers to the skin over the abdomen. The top record, *O*, is that from an animal given 144 mg. per kilogram (60 per cent of LD 50) of ortal-sodium intraperitoneally. The middle record, *E*, is that from another animal given 168 mg. per kilogram (60 per cent of LD 50) of evipal sodium intraperitoneally, and the bottom record the time in intervals of ten seconds. The rhythmic movements in the records are those of respiration superimposed on the main record. Each animal was stimulated as follows: 1. Rear foot pinched. 2. Forefoot pinched. 3 and 3'. Ear pinched. 4. Tail struck with a blunt object. 5, 6 and 7. Electrical excitation of one rear foot, forefoot and ear respectively. Contractions of the abdominal muscles are observed following each stimulation in the animal which received evipal as the anesthetic agent.

Evipal, being an ultrashort acting barbiturate, differs from all other members in the series. When studied by all available experimental methods, evipal without the aid of morphine does not produce anesthesia in rats, even when given in doses sufficient to kill 50 per cent of these animals. These animals become excited at first, show convulsive responses to noise and mechanical stimuli and later show deep hypnosis. Pinching the tail, ears or feet, inserting some fine object into the external auditory meatus, striking the tail a sudden blow with some blunt object, and electrical stimulation of the extremities, ears or tail provoke muscular movements, and if the pain is severe a sharp squeak is also audible. This lack of anesthesia can be seen in figure 2. In this experiment the animal, under 60 per cent of the LD 50 continued to respond to all forms of stimulation of the ear, feet and tail by contraction of the abdominal muscles. Similar findings have been observed with the use of LD 50.

Although the thiobarbiturates (pentothal and thioethamyl) will act as anesthetic agents when administered in adequate doses either to human beings or to most experimental animals, they produce strikingly different responses than do the barbiturates on organs other than the brain. With these, as with evipal, anesthesia cannot be produced in rats, but deep hypnosis results when they are injected intraperitoneally in LD 50.

In experimental animals, as well as in man, thioethamyl [7] and pentothal (thiopentobarbital) [8] may cause coughing, hiccuping and serious and annoying laryngospasm during anesthesia. Similar observations have been recorded with the use of evipal [9] as an anesthetic in human beings. Such changes have not been reported with the use of other barbiturates.

If large amounts of any of the barbiturates or thiobarbiturates are rapidly injected intravenously they will produce an abrupt fall in blood pressure and may in some cases cause sudden death by paralysis of the respiratory center (fig. 1). If, however, the thiobarbiturates are slowly injected intravenously in experimental animals (dog and monkey) in anesthetic doses, they do not produce a fall in blood pressure but may cause an increase in the systemic blood pressure of as much as 50 mm. of mercury [10] (figs. 3 and 6). Such increases in blood pressure accompanied usually by cardiac irregularities have never been observed following the injection of the barbiturates in our experiments nor have they been reported in the literature.

In their actions on the heart the thiobarbiturates differ from the barbiturates in a striking manner. The cardiac irregularity produced by the thiobarbiturates is closely associated with changes in blood pressure. If the control pressure is low, cardiac irregularity is not readily produced; however, if the pressure at the time of administration of the drug is high, irregularity is easily brought about. After pentothal anesthesia, any condition which will suddenly increase the arterial blood pressure also is apt to initiate this irregularity.

Before the tracing reproduced in figure 4 was made the animal had been given, intravenously, 20 mg. per kilogram of pentothal sodium, which caused cardiac arrhythmia of four and one-half minutes' duration. From this the heart had recovered spontaneously. At

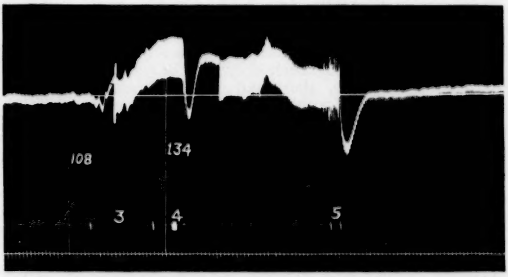


Fig. 3.—Dog 40. Weight, 8.5 Kg. Animal under light pentothal anesthesia. Top curve is that of the blood pressure with a mercury manometer, and the bottom record the time in intervals of fifteen seconds and zero blood pressure. Middle line indicates the time and speed of injection of drugs. At 3 the animal had recovered from the previous injection of the anesthetic agent and a second injection of sodium pentothal, 10 mg. per kilogram, was made intravenously. The blood pressure increased from 108 to 134 mm. of mercury and premature ventricular contractions are noted. Quinidine sulfate (17 mg.) was injected intravenously (at 4), causing a fall in blood pressure and temporarily restored normal cardiac rhythm. Amyl nitrite was inhaled at 5. Following this the blood pressure did not increase sufficiently to produce cardiac arrhythmia.

points 3, 4 and 5 in figure 4 the blood pressure was purposely increased by the removal of the carotid sinus reflex by clamping both carotid arteries. The first increase (at 3) took place six minutes after the injec-

7. Burstein, C. L., and Rovenstine, E. A.: Respiratory Parasympathetic Action of Some Shorter Acting Barbituric Acid Derivatives, J. Pharmacol. & Exper. Therap. **63**: 42 (May) 1938.

8. Lundy, J. S.: Intravenous Anesthesia, Am. J. Surg. **34**: 559 (Dec.) 1936.

9. Ménégaux and Sechehaye: Etude critique de l'anesthésie générale à l'évipan sodique, J. de chir. **44**: 363 (Sept.) 1934.

10. Reynolds, Chapman, and Veal, J. R.: Circulatory versus Respiratory Deaths from Pentothal Sodium, South. M. J. **31**: 650 (June) 1938. Gruber.[11] Gruber, Haury and Gruber.[11]

tion of the drug. It will be observed that, in succeeding attempts, as the anesthetic wears off the production of the arrhythmia becomes more difficult and when it is once produced it is of shorter duration. If the arrhythmia is present, any mechanical change which diminishes blood pressure or the injection of any chemical which will lower the arterial blood pressure will also cause the arrhythmia to disappear (figs. 3 and 6). We have taken electrocardiograms on 79 dogs which received anesthetic doses either of pentothal (thiopentobarbital) or of thioethamyl. The first change always noted in these electrocardiograms was a decrease in the PR interval (fig. 6). Shortly thereafter premature ventricular contractions (extrasystoles) were encountered either during or immediately after the completion of the injection in 55 animals, an incidence of more than 69 per cent. If we include also those second and third injections which are made for maintaining anesthesia, premature ventricular contractions were observed in 105 of the 143 injections, or 72 per cent.[11]

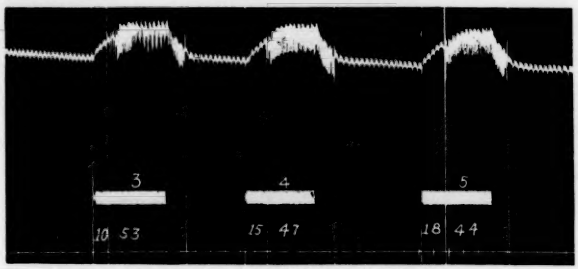


Fig. 4.—Dog 49. Weight, 10 Kg. Under pentothal sodium anesthesia (20 per mg. per kilogram). Top record that of the blood pressure with a mercury manometer, bottom record that of the time in ten second intervals. At 3, 4 and 5 the carotid sinus reflex was removed by clamping both carotid arteries. The elapsed time between clamping the carotid arteries and the production of cardiac irregularity in 3, 4 and 5 are ten, fifteen and eighteen seconds respectively. The duration of the irregularity once established lasted fifty-three, forty-seven and forty-four seconds respectively in 3, 4 and 5.

Cardiac arrhythmia following the injection of thiobarbiturates has been confirmed by Kohn and Lederer [12] and by Widenhorn, Volini and McLaughlin [13] in experimental animals. Although rarely seen, similar observations have been reported by Carraway [14] in human beings.

That pentothal has perhaps a direct toxic action on heart muscle was shown by Reynolds and Veal.[10] A comparison of the doses of digitalis necessary to kill experimental animals under thiopentobarbital anesthesia and other anesthetic agents would seem to add weight to their arguments.[15] In our laboratory with the use of U. S. P. reference digitalis powder, Gruber, Haury and Drake found the lethal dose of digitalis to be 89 mg. per kilogram when pentothal sodium (thiopentobarbital) was used as the anesthetic. This average is 16 mg. per kilogram, or 19 per cent, and 34 mg. per kilogram, or 38 per cent, less than the average doses found by us and the McGuigans [16] respectively, using sodium pentobarbital anesthesia. From these findings it would appear that great caution should be used in administering pentothal as an injection anesthetic to a patient taking digitalis, and in some cases its use might be contraindicated.

In 1925 De Waele [17] first showed that somnifene paralyzed the peripheral inhibitory mechanism to the heart. This finding has been extended to include all members of the barbiturate family.[18] The paralysis is apparently located at the postganglionic vagal nerve endings. However, with the use of the thiobarbiturates such depression has not been noted; indeed, if there is any effect on the heart it appears to make it more rather than less responsive to vagal impulses.[19] Slowing and inhibition of the heart can be obtained with a much weaker electrical stimulus applied to the vagal nerve trunk after the administration of a thiobarbiturate than in undrugged animals.

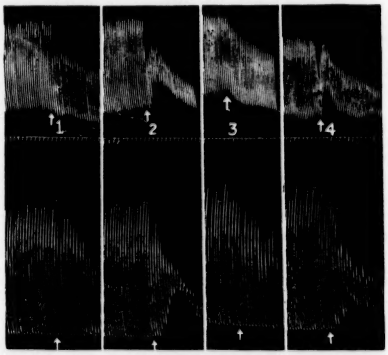


Fig. 5.—Excised longitudinal segments of rabbit intestine. Top record is that of the duodenal segment and the bottom curve is that of the ileal segment. Time in intervals of ten seconds. Tyrode's solution with a *p*H of 7.6 to 7.8 was used as the bath and oxygenated by bubbling air through it. The concentration of the drug in each case is a 1: 20,000 dilution. 1. Thioethamyl sodium. 2. Thiopentobarbital sodium (pentothal). 3. Sodium pentobarbital. 4. Thiopentobarbital sodium (pentothal). Pentothal increases the general tonus but decreases the force of the contractions.

11. Gruber, C. M.: The Effects of Anesthetic Doses of Sodium Thiopentobarbital, Sodium Thioethamyl and Pentothal Sodium upon the Respiratory System. The Heart and Blood Pressure in Experimental Animals, J. Pharmacol. & Exper. Therap. **60:** 143 (June) 1937. Gruber, C. M.; Haury, V. G., and Gruber, C. M., Jr.: The Cardiac Arrythmia, Characteristic Effect of the Thiobarbiturate (Pentothal, Thiopentobarbital and Thioethamyl) as Influenced by Changes in Arterial Blood Pressure, ibid. **63:** 193 (June) 1938.

12. Kohn, Richard, and Lederer, Ludvig: Pentothal Studies with Special Reference to the Electrocardiogram, J. Lab. & Clin. Med. **23:** 717 (April) 1938.

13. Widenhorn, H. L.; Volini, I. F., and McLaughlin, R. F.: The Effect of General, Local and Intravenous Anesthetics on the Experimental Electrocardiogram, Anesth. & Analg. **17:** 96 (March-April) 1938.

14. Carraway, B. M.: Pentothal Sodium with Nasal Oxygen, Anesth. & Analg. **18:** 266 (Sept.-Oct.) 1939.

15. Gruber, C. M.; Haury, V. G., and Drake, M. E.: The Toxicity of Digitalis and Ouabain in Animals Under Sodium Thiopentobarbital and Sodium Pentobarbital Anesthesia, Am. Heart J. **20:** 329 (Sept.) 1940.

16. McGuigan, R. A., and McGuigan, H. A.: The Use of Dogs for the Standardization of Digitalis, J. Pharmacol. & Exper. Therap. **63:** 76 (May) 1938.

17. De Waele: L'action de doses élevées des dérivés barbituriques sur le pneumogastrique, Arch. internat. de physiol. **25:** 83, 1925.

18. Gruber, C. M.; Haury, V. G., and Gruber, C. M., Jr.: The Depressant and Paralytic Actions of the Barbiturates on the Terrapin Cardiac Vagus Nerve, J. Pharmacol. & Exper. Therap. **63:** 229 (July) 1938; The Point of Action of the Barbiturates in Depressing the Cardiac Vagus Nerves, ibid. **63:** 239 (July) 1938.

19. Gruber, C. M.; Gruber, C. M., Jr., and Colosi, N. A.: The Irritability of the Cardiac Vagus Nerves as Influenced by the Intravenous Injections of Barbiturates, Thiobarbiturates and Picrotoxin, J. Pharmacol. & Exper. Therap. **63:** 215 (July) 1938.

That the barbiturates depress intestinal muscle whether intact or excised is a well known fact. The same uniformity of action is not produced with the use of the thiobarbiturates.[20] Indeed, if dilute solutions of ments of experimental animals (fig. 5). Moderate concentrations cause an increase in the general tonus and a decrease in the force of the contractions, and high concentrations a temporary increase in general tonus

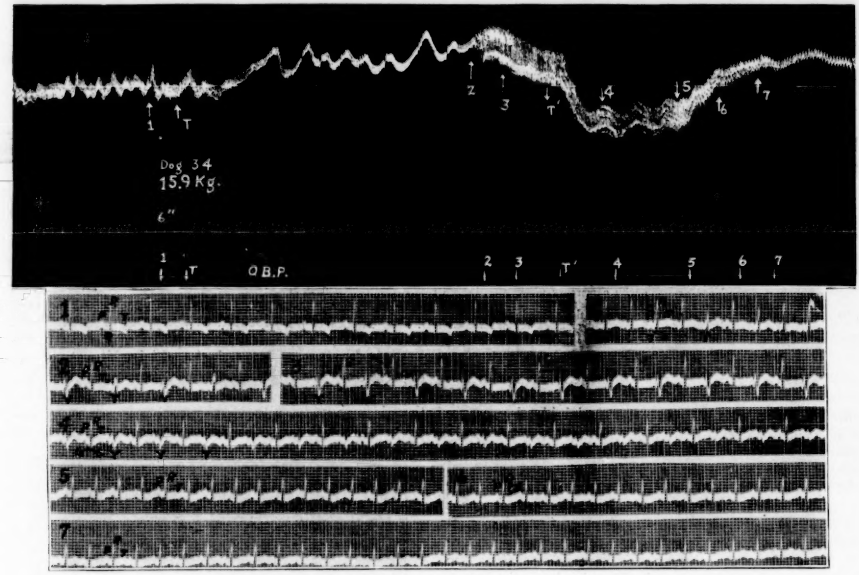
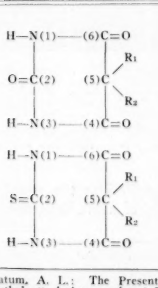


Fig. 6.—Dog 34. Weight, 15.9 Kg. Morphine sulfate 5 mg. per kilogram was administered subcutaneously, and ether anesthesia was used in the preparation of the animal. Top record is that of the blood pressure taken from the carotid artery with a mercury manometer, heparin being used as the anticoagulant. Bottom line indicates zero blood pressure, the time and speed of injection of pentothal sodium and the points at which electrocardiograms were taken. Middle record, the time in intervals of six seconds. The animal was permitted to become lightly anesthetized with ether at 1 and the ether was withdrawn at T, when the injection of 20 mg. per kilogram (318 mg.) of pentothal sodium was started. This was completed at T′. Four minutes later premature ventricular contractions are seen in electrocardiograms 2, 3 and 4 at Y.

Electrocardiograms	1	2	3	4	5	6	7
Heart rate	130	195	210	220	210	225	220
PR interval in 1/25 second	3	2	2.5	2.5	3	3	3

During the injection of pentothal the blood pressure increased from 124 to 152 mm. of mercury.

A Modified Plan of Classification of Barbituric Acid Derivatives *



		5 R1	R2
Long	Phenobarbital U. S. P. (Luminal)	ethyl	phenyl
	Barbital U. S. P. (Medinal) (Veronal)	ethyl	ethyl
Intermediate	Neonal N. N. R.	ethyl	n-butyl
	Dial N. N. R.	allyl	allyl
	Ipral N. N. R.	ethyl	isopropyl
	Alurate N. N. R.	allyl	isopropyl
	Nostal N. N. R.	bromallyl	isopropyl
	Amytal N. N. R.	ethyl	isoamyl
	Sandoptal N. N. R.	allyl	isobutyl
Short	Pentobarbital U. S. P. (nembutal)	ethyl	1-methyl butyl
	Phanodorn N. N. R.	ethyl	cyclohexenyl
	Ortal N. N. R.	ethyl	n-hexyl
Ultra Short	Evipal †	methyl	cyclohexenyl
Sulfur Derivatives	Thioethamyl	ethyl	isoamyl
	Thiopentobarbital (pentothal)	ethyl	1-methyl butyl

* Tatum, A. L.: The Present Status of the Barbiturate Problem, Physiol. Rev. **19**: 487 (Oct.) 1939.
† Methyl attached to number 1 N.

the thiobarbiturates are used they usually cause an increase in the general tonus in excised intestinal seg- followed by a marked decrease. In unanesthetized experimental animals with Thiry-Vella loops the thiobarbiturates in anesthetic doses invariably cause a temporary disappearance of the contractions and a decrease in the general tonus of the intestine which persist as long as the animals remain anesthetized.

20. Gruber, C. M., Jr., and Gruber, C. M.: Segments of Excised Small Intestine as Affected by the Sodium Salts of Thioethamyl, Thiopentobarbital, Pentobarbital and Evipal, Arch. internat. d. pharmacodyn. et de thérap. **63**: 243 (Nov. 30) 1939.

In similar experimental animals with permanent gastric and duodenal fistulas the barbiturates in anesthetic doses cause complete inactivity of the stomach and pylorus with a decrease in the general tonus of both. A similar change is usually noted with the use of the thiobarbiturates; however, the results are more variable and indeed in some experiments an increase in the general tonus of both organs is sometimes noted.[21]

Whether habituation or tolerance can be acquired by man with the thiobarbiturates as with the barbiturates has not thus far been determined. The pathologic changes in tissues following the injection of large doses of thiobarbiturates are apparently the same as those resulting from the administration of large doses of any barbiturate.[22]

In this short paper I have attempted to present certain changes which follow barbiturate and thiobarbiturate administration in human beings and in experimental animals. Although differences in duration of action of the barbiturates on the central nervous system have been emphasized in the literature, they are, however, not the only results to be observed. Striking variations in effects of the two groups of drugs are to be expected both in experimental animals and in human beings.

THE APPLIED PHYSIOLOGY OF BILE SECRETION AND BILE SALT THERAPY

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Numerous questions arise in the mind of the clinician and physiologist regarding the regulation of bile salt output and the rational therapeutic use of bile salts in hepatic and biliary tract disease. My associates and I have sought to answer some of these questions by studies on animals, since patients with a total bile fistula are scarce and none have been available to us. In addition, there are certain questions which cannot be answered by clinical observation.

FOOD

It has been clearly established that protein stimulates the formation of bile and bile salt production.[1] The situation with regard to fat and sugar is not so clear. There is no evidence showing that fat and sugar increase bile salt production; the available evidence is to the contrary. When sugar is given to a fasting biliary fistula animal that is receiving no bile salts enterally, cholic acid and bile volume output is reduced. The same is usually true after several repeated feedings of olive oil. When fat and sugar are added to a mixed diet containing adequate protein, the bile output is not significantly changed.[1] Our studies confirm the conclusions of Smith and Whipple, namely that there is no direct relationship between bile salt output and the caloric value of the diet, and that food protein is of primary importance in determining the level of bile salt synthesis.

WILL FREQUENT MEALS IN THE ABSENCE OF THE GALLBLADDER INCREASE BILE FORMATION?

In order to answer the question Will frequent meals in the absence of the gallbladder increase bile formation? it is necessary to keep the daily intake of protein, fat and carbohydrate constant. When this is done, feeding more frequently than every six hours does not increase bile output. The rate of formation and flow of bile, however, is more constant when the daily diet is ingested every six hours than when taken as three conventional meals.

Whether frequent feeding augments the output of bile in an animal with a normal gallbladder is uncertain. The answer to this question is not so simple as it appears to be on first thought. If with a gallbladder in place a meal did not cause it to empty, then the stored bile salt would not be evacuated and the bile formed after the meal would be considerably less. Keeping the daily food intake constant, evacuation of the gallbladder three times a day should result in more bile being formed than evacuation once a day. It does not follow, however, that evacuation four times a day will cause more bile to be formed than evacuation three times a day. This is because each time a certain quantity of bile salt traverses the enterohepatic circuit approximately 10 per cent of it is "lost."[2] This observation raises an old question, namely "How is the bile salt output of the liver regulated?"

REGULATION OF BILE SALT OUTPUT BY THE LIVER

The rate of production of bile salts balances the rate of "destruction." This has been recently demonstrated by us[3] in the following manner: A bile fistula animal is placed on a basal ration which is fed every eight hours without the return of bile to the intestine. After the animal has been under this condition for several days, the bile secreted during the previous eight hour period is returned, and then all bile is returned every eight hours thereafter. When this is done the bile salt output in the bile accumulates until a plateau or level is reached. At this relatively stable level, production and "destruction" of bile salt are in balance (chart 1). If, when bile is initially returned to the intestine, a large amount of bile salt, such as 6 Gm., is introduced, then the bile salt output is reduced until a relatively constant level is reached (chart 2). This phenomenon may be expressed by a mathematical equation.[3] The variables are time, the amount of cholic acid destroyed (10 per cent) and the amount of cholic acid formed, which depends primarily on the protein metabolism.

"Sluice mechanism." What happens to the "lost" or "destroyed" bile salt is unknown. It is known that, if too much bile salt is introduced into the intestine at any period, catharsis is produced. It is possible that, in the presence of catharsis, bile salt is passed into the colon or in the feces. However, we have not been able to detect cholic acid in the feces or to recover quantita-

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21. Gruber, C. M., and Gruber, C. M., Jr.: The Effect of Barbituric and Thiobarbituric Acid Derivatives on the Pyloric Sphincter and Stomach in Unanesthetized Dogs, J. Pharmacol. & Exper. Therap. **72:** 176, 1941.

22. Gruhzit, O. M.; Dox, A. W.; Rowe, L. W., and Dodd, M. C.: A Pharmacologic Study of Certain Thiobarbiturates, J. Pharmacol & Exper. Therap. **60:** 125, 1937. Reynolds, Chapman; Schenken, J. R., and Veal, J. R.: Pathologic Findings in Mice After Pentothal Narcosis, Anesth. & Analg. **17:** 357 (Nov.-Dec.) 1938.

From the Department of Physiology and Pharmacology, Northwestern University Medical School.

Read before the Section on Pathology and Physiology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 4, 1941.

1. Smith, H. P., and Whipple, G. H.: Bile Salt Metabolism, J. Biol. Chem. **80:** 671, 1928. Kocour, E. J., and Ivy, A. C.: The Effect of Certain Foods on Bile Volume Output Recorded in the Dog by a Quantitative Method, Am. J. Physiol. **122:** 325, 1938.

2. Schmidt, C. R.; Beazell, J. M.; Berman, A. L.; Ivy, A. C., and Atkinson, A. J.: Studies on Bile Secretion, Am. J. Physiol. **126:** 120, 1939.

3. Berman, A. L.; Snapp, E.; Ivy, A. C., and Atkinson, A. J.: On the Regulation or Homeostasis of the Cholic Acid Output in Biliary-Duodenal-Fistula Dogs, Am. J. Physiol. **131:** 776, 1941.

tively cholic acid added to the feces by means of the Gregory-Pascoe method.

We have recently simulated in the bile fistula dog the condition that obtains in the cholecystectomized patient. This was done as in the preceding experiment, except that the bile formed every hour was returned. That is, bile was being collected and returned continuously, which is analogous to the continuous flow of bile into the intestine of the cholecystectomized patient. Under these conditions a plateau is reached, as in the preceding experiment, but it is attained sooner, namely in about twenty-four one hour periods instead of twenty-four eight hour periods.

The particular homeostatic level maintained probably depends on the protein content of the diet.[1] This indicates that, to maintain a good rate of flow of bile through the bile passages in the cholecystectomized patient, the amount of protein in the diet should not be low. This may explain why some cholecystectomized patients continue to be intolerant to "rich" (fat and sugar) foods after cholecystectomy, though one should not forget the role that the sphincter of Oddi and a chronic pancreatitis may play in this regard. However, given an adequate protein diet with other conditions normal, the cholecystectomized subject probably should circulate more bile through the bile ducts daily than a subject with a normal gallbladder.

TABLE 1.—*Bile Salts*

Bile Salts	Per Cent Increase in Volume Output of Bile Over Basal Control
3 Gm. sodium cholate	80
3 Gm. sodium cholate as tauro and glycocholate	36
3 Gm. sodium dehydrocholate oxidized cholic acid	106
3 Gm. sodium dehydrocholate as tauro and glycocholate	39
3 Gm. sodium deoxycholate	74
3 Gm. sodium dehydrodeoxycholate	81
3 Gm. sodium lithocholate	−21*
3 Gm. sodium dehydrolithocholate	−40*
3 Gm. desiccated ox bile salts	33
3 Gm. desiccated hog bile salts	38
3 Gm. sodium hyodeoxycholate; chief acid in hog bile	38
3 Gm. sodium dehydrohyodeoxycholate; oxidized H. B. acid	33
3 Gm. sodium glycodehydrohyodeoxycholate; conjugated oxidized hog bile acid	30

* Inhibited bile secretion.

DOES THE CHOLERETIC ACTION OF THE VARIOUS PREPARATIONS OF BILE SALTS DIFFER?

The various bile salt preparations available for use in man differ in chemical structure. Hence, they may differ in regard to their choleretic properties (table 1).

Ox bile salts (conjugated unoxidized cholic acid) and hog bile salts in 3 Gm. doses increase the volume output of bile about 30 per cent in the dog with a normal liver. Ox bile contains the bile salts found in human bile, and all but 10 per cent of that given is excreted in the bile. Hog bile contains a bile salt, a salt of hyodeoxycholic acid, that it not present in human or dog bile.[4] Whether the hog bile acid is as suitable as ox bile acids for man is uncertain; a lack of suitability has not been demonstrated.

Dehydrocholic acid or oxidized unconjugated cholic acid is definitely hydrocholeretic. If the taurin and glycin are removed from taurocholic and glycocholic acid and the remaining cholic acid is oxidized, the product is oxidized, unconjugated cholic acid, or dehydrocholic acid. It is referred to as triketocholanic acid and its salt as a triketocholanate, because the 3 C—OH, or hydroxy groups in cholic acid are changed to C=O, or keto groups. The bile formed in response to dehydrocholic acid is truly thin bile. It is less viscous and contains less total solids per cubic centimeter of bile. The normal output of the natural bile salts, sodium taurocholate and glycocholate, is not significantly affected.[4]

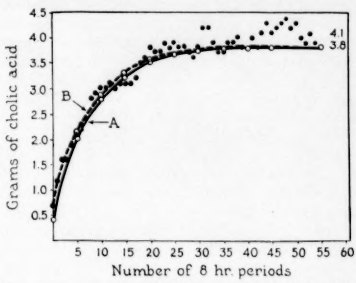

Chart 1.—Average curve predicted by mathematical equation of output of cholic acid in animals when the initial amount of bile and bile salt returned was that which was secreted the previous eight hour period when no bile was being returned. After the initial return all bile formed was returned, except a small sample for analysis. The dots indicate the actual output.

Since oxidized bile salts are hydrocholeretic, increase the amount of keto-reacting substances in the bile [5] and are given clinically over rather long periods of time, the question of their possible toxicity has been considered. From 3 to 5 Gm. daily of oxidized bile salts were fed to dogs for from three to seven months and 0.3 Gm. per kilogram daily to white rats for one month. Observations on the body weight, dye clearance and total fat and glycogen content of the liver failed to reveal evidence of toxicity under the conditions of the experiments.[6] A study of the toxicity of various bile acids, as measured by the hemolysis of red blood cells and the depression of blood pressure on intravenous

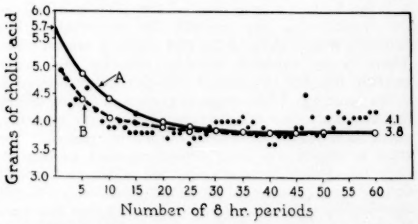

Chart 2.—The same as chart 1 except that the initial introduction of cholic acid as bile amounted to 5.7 Gm. Curve *B* in both charts is the curve predicted when the curve is calculated from the amount of cholic acid introduced at the start of the second eight hour period. When the intestine has not been receiving bile salts, it is apparently sensitive to large doses and more than the usual 10 per cent is "lost" for the first enterohepatic circuit.

4. Berman, A. L.; Snapp, E.; Ivy, A. C.; Hough, V. H., and Atkinson, A. J.: The Effect of Desiccated Hog Bile and Hog Bile Acid Preparations on the Volume and Constituents of Bile, Am. J. Physiol. **131**: 752, 1941. Berman, Snapp, Ivy, Atkinson and Hough.[5]

5. Berman, A. L.; Snapp, E.; Ivy, A. C.; Atkinson, A. J., and Hough, V. H.: The Effect of Various Bile Acids on the Volume and Certain Constituents of Bile, Am. J. Digest. Dis. **7**: 333, 1940.

6. Berman, A. L.; Snapp, E.; Ivy, A. C., and Atkinson, A. J.: The Effect of Long-Continued Ingestion of Oxidized Bile Acids on the Dog and Rat, Am. J. Digest. Dis. **7**: 280, 1940.

administration, revealed that sodium dehydrocholate or triketocholanate was the least toxic of the bile acids studied.[7]

DO THE BILE SALTS INFLUENCE HEPATIC BLOOD FLOW?

To study the effect of bile salts on the blood flow to the liver, we used the thermostromuhr method of Baldes and Herrick.[8] It was found that oxidized unconjugated bile salt, or sodium dehydrocholate or triketocholanate, very definitely and uniformly increased the blood flow through the hepatic artery. Other bile salts did not have such an effect. An increase in hepatic arterial blood flow would tend to increase the oxygen supply to the liver; the utility of this is at present conjectural.[9]

THE ABNORMAL LIVER

It is now well known that, in the presence of severe hepatitis, cholic acid disappears from the fluid drained from the bile duct. It is also known that, after the release of an obstruction of the common bile duct, several days to a week or more may elapse before cholic acid reappears in the drainage, and the output of cholic acid returns to normal. According to our observations, when hepatitis is so severe that cholic acid is not formed, the administration of bile salts does not cause a choleresis and the administered cholic acid is not eliminated in the bile. This raised the question Is the administration of bile salts injurious in the presence of obstructive jaundice and hepatitis? Clinically bile salts have been administered for short periods without any evidence of harm being observed. We have not found any evidence in the literature regarding the effect of prolonged administration of bile salts in the presence of complete obstruction. Accordingly, an experiment has been done to obtain some evidence regarding the question.

Thirteen dogs in which the common duct was obstructed and to which no bile salts were administered survived an average of twenty-five days. Seventeen dogs in which the common duct was obstructed and to which 2 Gm. of ox bile salts was given orally daily survived an average of twenty-eight days. Because of the wide variation in longevity after complete obstruction of the common duct, these results cannot be considered as conclusive. Yet, if the administration of bile salts in the presence of obstructive jaundice is definitely harmful, some difference between the average longevity of the two groups of animals should have been observed.

The metabolism of bile salts administered in the presence of obstruction of the common bile duct, according to our knowledge of the literature, has not been adequately studied.

DOES THE ADMINISTRATION OF BILE SALTS AFTER THE RELIEF OF OBSTRUCTION OF THE COMMON BILE DUCT INCREASE THE CLEARANCE OF JAUNDICE?

Much evidence on dogs clearly demonstrates that choleresis under normal conditions does not increase pigment output. Neither does a choleresis increase the rate of clearance of intravenously injected bilirubin.[10] Such observations, however, may not apply to the clearance of jaundice after the relief of obstruction of the common bile duct.

It has been suggested by clinical observation that the use of sodium dehydrocholate facilitates the recovery from jaundice due to obstruction[11] and arsenical hepatitis.[12] Obviously it is difficult, if not impossible, to control adequately such observations.

We[13] have attacked the problem by producing an obstruction of the common bile duct in 20 dogs. The obstruction was released after seven days, and a biliary fistula made. One group of 10 animals received sodium dehydrocholate (3 Gm. daily) and the other served as controls. We studied the rate of disappearance of bile pigment from the blood and urine and the time of return of cholic acid production to the average normal value. The results showed that the administration of the bile salt had no definitely significant effect on the rate of clearance of the jaundice (table 2). Even under controlled laboratory conditions, the rate of recovery of the liver from the effects of obstruction and of the clearance of jaundice is subject to considerable variation. This renders it impossible, without performing many tests, to draw an accurate conclusion.

TABLE 2.—*Comparison of Average Results Obtained in the Control and Bile Salts Groups*

No. of Dogs	Weight, Kg.	Days of Observation	Regimen	Blood Bilirubin: Preoperative, Mg. per 100 Cc.	Blood Bilirubin: Normal in Days	Urine Bilirubin: Preoperative, Mg. per 100 Cc.	Urine Bilirubin: Normal in Days	Cholic Acid: Mg. per 24 Hrs.	Cholic Acid: Normal in Days	Diet Normal in Days
10	10.4	7	Control	8.9	6.0	13.9	5.0	1,187	5.0	3
			Average range	2.8-24.8	4-13	8.1-24.0	3-12		3-10	
10	9.9	7	3 Gm. ketocholate per day	6.7	5.0	8.5	4.0	1,136	5.0	3
			Range	4.5-9.0	4-7	2.2-21.0	3-6		3-7	

DOES A CHOLERESIS "FLUSH-OUT" THE GALLBLADDER?

It is obvious that the production of choleresis should flush the bile ducts. It does not follow, however, that a choleresis will flush out the gallbladder.

To answer this question, 10 Gm. of sand particles varying in size from 0.5 to 1 mm. in diameter were

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8. Baldes, E. J., and Herrick, J. F.: A Thermostromuhr with Direct Current Heater, Proc. Soc. Exper. Biol. & Med. **37:** 432, 1937.

9. Grodins, F. S.; Osborne, S. L.; Ivy, A. C., and Goldman, L.: The Effect of Bile Acids on Hepatic Blood Flow, Am. J. Physiol. **132:** 375, 1941.

10. Berman, A. L.; Snapp, E., and Ivy, A. C.: The Effect of Choleresis on the Rate of Excretion of Intravenously Injected Bilirubin, Am. J. Physiol. **132:** 176, 1941.

11. Boyce, F. F.: Hepatic and Biliary Tract Disease, Ann. Surg. **109:** 351, 1939. Boyce, F. F., and McFetridge, E. M.: Studies on Hepatic Function by the Quick Hippuric Acid Test: Biliary and Hepatic Disease, Arch. Surg. **37:** 401 (Sept.) 1938. Finsterer, Hans: Surgical Treatment of Acute Cholecystitis and Common Duct Obstruction, Surgery **6:** 491, 1939.

12. Appel, Bernard: Sodium Dehydrocholate in Arsphenamine Poisoning, Arch. Dermat. & Syph. **27:** 401 (March) 1933. Appel, Bernard, and Jankelson, I. R.: Treatment of Arsenical Hepatitis with Sodium Dehydrocholate: Experimental and Clinical Studies in Cases of Arsphenamine Poisoning, ibid. **32:** 422 (Sept.) 1935.

13. Berman, A. L.; Snapp, E., and Ivy, A. C.: The Effect of Bile Salts on Recovery of Liver Function After Release of Common Duct Obstruction, Surgery, to be published.

placed aseptically in the gallbladder. The sand was intended to represent biliary sediment. It was opaque to roentgen rays; thus, its rate of disappearance from the gallbladder could be studied.

Sixty dogs were used: Group 1. Fifteen of the animals served as controls. They were fed a mixed meal four times daily (every six hours). The sand disappeared from the gallbladder in an average of eighteen days; range, ten to thirty-one days. Group 2. Fifteen animals were treated like the controls, except that they were given 0.5 Gm. of ketocholanates with each meal. This dose of ketocholanates is known to cause a hydrocholeresis. The sand disappeared from the gallbladder in an average of seventeen days; range, eight to thirty-three days. Group 3. Fifteen animals were given 125 cc. of half and half egg yolks and cream four times daily. The sand disappeared in an average of ten days; range, six to fifteen days. Group 4. Fifteen animals received the egg yolks and cream plus 0.5 Gm. of ketocholanates. The sand disappeared in an average of eight days; range, four to fourteen days.

The results of these experiments, conducted by Drs. H. Wigodsky and B. P. Phibbs in my laboratory, show that choleresis per se does not have a significant flushing action of the gallbladder. However, they show definitely that the frequent administration of egg yolks and cream augments the rate of passage of sand from the gallbladder. Thus, in the presence of normal formation of bile, frequent evacuation of the gallbladder facilitates the removal of sediment from the viscus. If bile had not been adequately formed, then bile salts probably would have been of benefit. In these experiments on normal animals the administration of bile salts was superfluous.

SUMMARY

1. Protein promotes the formation of bile and cholic acid in the dog, a fact that is worthy of consideration in the management of cholecystectomized patients.

2. Bile salt output is maintained at a relatively constant level because the rate of production is balanced by the rate of "destruction." The rate of production depends primarily on the amount of protein metabolized and the rate of destruction on the rate of enterohepatic circulation of a particular quantity of cholic acid. About 10 per cent of a quantity of cholic acid is lost during each enterohepatic circuit. Excessive bile salt causes catharsis, which increases the loss ("sluice mechanism"). Given a high protein diet and otherwise normal conditions, a cholecystectomized subject probably should pass a larger volume of bile through the common duct than a subject with a normal gallbladder.

3. Oxidized cholic acid (dehydrocholic or triketocholanic acid) is a hydrocholeretic agent. The bile formed is less viscous and contains less total solids per cubic centimeter than the bile formed in response to glycocholic and taurocholic acid.

4. Sodium dehydrocholate quite consistently increases the rate of blood flow through the hepatic artery. This is not true of sodium cholate, glycocholate and taurocholate.

5. Evidence showing that the daily administration of bile salts in the presence of complete obstruction of the common bile duct is harmful was not obtained.

6. Definite evidence that the administration of sodium dehydrocholate speeds the rate of recovery from obstructive jaundice after the release of the obstruction was not obtained.

7. The production of choleresis obviously flushes the bile ducts but does not flush the gallbladder. However, in the presence of normal formation of bile, frequent evacuation of the gallbladder facilitates and speeds the removal of sediment (represented by sand in our experiments) from the viscus.

MASSIVE DOSE ARSENOTHERAPY OF EARLY SYPHILIS BY INTRAVENOUS DRIP METHOD

RECAPITULATION OF THE DATA (1933 TO 1941)

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LOUIS CHARGIN, M.D.
AND
HAROLD THOMAS HYMAN, M.D.
NEW YORK

Previous papers have dealt with the pharmacologic work underlying the adoption of the continuous intravenous drip method,[1] the clinical results in earlier series,[2] the organization of the supervisory committee,[3] the technical considerations for the administration of the drug,[4] the serologic [5] and chemical studies,[6] the organization of the follow-up clinic, under the direction of Dr. Evan Thomas [7] and Dr. Bruce Webster,[8] and the public health aspects.[9]

THE PLAN OF STUDY

Four groups of patients are included in the present summary (table 1).

Group 1, studied in 1933, consisted of 25 patients [2] who were given an average of 4 Gm. of neoarsphenamine over the course of five days.

Read before the Section on Dermatology and Syphilology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 5, 1941.

From the Department of Health of the City of New York (Dr. John L. Rice, Commissioner) and the First Medical Service of the Mount Sinai Hospital (Dr. George Baehr, Attending Physician).

This work has been supported by the New York Foundation, The Friedsam Foundation, Inc., The John and Mary R. Markle Foundation and the late Ernst Rosenfeld. The monies were administered by the Committee on Neighborhood Health Development (Mr. Kenneth Widdemer, Director).

The supervisory committee included Dr. John L. Rice; Dr. Theodore Rosenthal, representing the Department of Health; Dr. John Mahoney, of the United States Public Health Service; Dr. Walter Clarke, of the American Social Hygiene Association; Dr. Walter W. Palmer and Dr. Charles C. Lieb, of Columbia University; Dr. Eugene Du Bois and Dr. Bruce Webster, of Cornell University; Dr. Evan Thomas, of Bellevue Hospital; Dr. George Baehr, of Mount Sinai Hospital, and Drs. Leifer, Chargin and Hyman.

1. Hirshfeld, Samuel; Hyman, H. T., and Wanger, Justine J.: Influence of Velocity on Response to Intravenous Injections, Arch. Int. Med. **47**: 259 (Feb.) 1931.

2. Chargin, Louis; Leifer, William, and Hyman, H. T.: Studies of Velocity and Response to Intravenous Injections: Application of Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in Treatment of Early Syphilis, J. A. M. A. **104**: 878 (March 16) 1935. Hyman, H. T.; Chargin, Louis, and Leifer, William: Massive Dose Arsenotherapy of Syphilis by Intravenous Drip Method: Five Year Observations, Am. J. M. Sc. **197**: 480 (April) 1939. Footnote 10.

3. Baehr, George: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method: The Preliminary Work with Neoarsphenamine, Arch. Dermat. & Syph. **42**: 239 (Aug.) 1940.

4. Leifer, William: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method: Technic, Arch. Dermat. & Syph. **42**: 246 (Aug.) 1940.

5. Mahoney, J. F.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method: Résumé of Serologic Observations, Arch. Dermat. & Syph. **42**: 263 (Aug.) 1940.

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9. Rice, J. L.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, Arch. Dermat. & Syph. **42**: 278 (Aug.) 1940.

Group 2, studied in 1938, comprised 86 men [10] treated in the same manner.

Groups 1 and 2 constitute the neoarsphenamine series of 111 patients.

Group 3, studied in 1938 and 1939, included 157 syphilitic patients. These men received mapharsen [11] in doses varying between 400 and 1,100 mg., the average approximating 700 mg.

Group 4 consisted of 118 patients treated late in 1939 and early in 1940. These patients received 1,200 mg. of mapharsen.[11] Four are also reported in the neoarsphenamine series. They were retreated with mapharsen: 3 for reinfections and 1 for infectious relapse.

EVOLUTION OF TREATMENT

The evolution of the treatment of the four groups was dependent on the clinical and serologic experiences.

Neoarsphenamine was abandoned because of a fatal complication of treatment and the high incidence of peripheral neuritis.

In the earlier mapharsen group, the frequent occurrence of infectious relapse and the safety of the drug (as evidenced by the low incidence of toxicologic manifestations) led to a gradual and probative elevation of the dose of the arsenical. The initial amount of 400 mg. was increased to what seemed a safe and optimal total of 1,200 mg. administered over the course of five days. Group 3 includes the patients who were given less than the optimal, safe dose of 1,200 mg. Group 4 includes all who received the optimal amount.

Despite the variations in the type and doses of drug, the entire clinical experience is presented as a unity. Significant variations are indicated.

CLINICAL DATA

Sex.—With one exception, all patients were male. The exclusion of females was necessitated by our facilities, which consisted of beds in a male ward in the Mount Sinai Hospital.

TABLE 1.—*Classification of Patients Treated*

Group	Drug	Year of Treatment	Number of Patients	Stage of Disease: Sero-Negative Primary	Stage of Disease: Sero-Positive Primary	Stage of Disease: Secondary
1	Neoarsphenamine, 4 Gm.	1933	25	1	24	
2	Neoarsphenamine, 4 Gm.	1938	86	11	38	37
3	Mapharsen, 0.4-1.1 Gm.	1938-1939	157	18	59	80
4	Mapharsen, 1.2 Gm.	1939-1940	118*	16	45	57
Total number			386†	46	340	
Percentage			100	12	88	

* Includes 4 men of series 2.
† Whole number of individual patients is 382.

Age.—The age of the patients varied from 13 to 56. The majority were in the range between 20 and 35.

Race.—Of the patients 233 were white, 161 were Negroes and 2 were Chinese. The incidence of failure of treatment was somewhat higher among the Negroes. There were no significant differences in toxicity.

Stage of the Disease.—Forty-six (12 per cent) of the men, on admission, were in the seronegative primary stage, most favorable from a therapeutic outlook. The diagnosis of syphilis in each of these was established by dark field examinations performed in the clinic of the referring institution and at the Mount Sinai Hospital.

TABLE 2.—*Complications Frequently Encountered*

	Neoarsphenamine Series	Mapharsen Series
Local venous reactions	Infrequent, but not tabulated	
Primary fever	69 (62%)	119 (39%)
Secondary fever	71 (64%)	39 (13%)
Toxicoderma	50 (45%)	35 (12%)
Peripheral neuritis	39 (35%)	5 (1.7%)
Nausea and vomiting	Frequent, but not tabulated	

The 25 patients in group 1 were not classified as to the stage of the disease, with the exception of 1, who was in the seronegative primary stage. The others had seropositive primary or secondary syphilis.

Of the patients in groups 2, 3 and 4, 142 were in the seropositive primary stage and 174 in the secondary phase. Thus the series was heavily weighted with patients in the later stages of early syphilis, less amenable to specific chemotherapy than those with seronegative primary syphilis.

TOXICITY

1. *Mild Symptoms (Table 2).*—A. Local Reactions: On rare occasions localized phlebitis was observed. At worst, this was mild. The low incidence of this complication was probably the result of two technical factors: (1) the use of the veins of the forearm in place of those in the antecubital fossa and (2) the practice of inserting the needle to the hilt.

B. Nitritoid Crises: Inclusive of the infusions done in retreatment, 2,045 separate infusions were made. Nitritoid crises were never seen. This would seem definitively to establish the original hypothesis of the identity of nitritoid crises and "speed shock." [1]

C. Primary Fever: Forty-eight per cent of the patients had primary fever. The incidence of this complication was higher with neoarsphenamine (62 per cent) than with mapharsen (39 per cent).

In the neoarsphenamine series a number of patients were given large doses of thiamine hydrochloride and ascorbic acid. There was a slightly decreased incidence of primary fever among those who received the vitamins.

Curiously, the group given large doses of mapharsen experienced a somewhat lower incidence of primary fever than those who received the smaller doses.

D. Secondary Fever: Somewhat less than 30 per cent of all the patients experienced secondary fever. The incidence with neoarsphenamine was 64 per cent, compared to 13 per cent with mapharsen. The vitamin-treated patients showed no appreciable diminution in the toxic complication.

E. Toxicoderma: Toxicoderma, which usually accompanied the secondary fever, showed the same general distribution as the febrile disturbance. The

10. Hyman, H. T.; Chargin, Louis; Rice, J. L., and Leifer, William: Massive Dose Chemotherapy of Early Syphilis by Intravenous Drip Method, J. A. M. A. **113:** 1208 (Sept. 23) 1939. Hyman, H. T.; Chargin, Louis, and Leifer, William: Massive Dose Arsenotherapy of Syphilis by Intravenous Drip Method, Am. J. Syph., Gonor. & Ven. Dis. **23:** 685 (Nov.) 1939.

11. Chargin, Louis: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method: Toxicologic Manifestations, Arch. Dermat. & Syph. **42:** 249 (Aug.) 1940. Hyman, H. T.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method: Clinical Considerations, Arch. Dermat. & Syph. **42:** 254 (Aug.) 1940.

incidence was 45 per cent with neoarsphenamine and 12 per cent with mapharsen.

F. Peripheral Neuritis: Peripheral neuritis occurred in 35 per cent of the patients given neoarsphenamine. The use of mapharsen reduced the incidence of this complication to zero in the group receiving small doses, to 3.7 per cent in the group receiving large doses and to 1.7 per cent in the two groups together.

TABLE 3.—*Grave Complications Infrequently Encountered*

	Neoarsphenamine Series	Mapharsen Series
Jaundice	4 (3.6%)	2 (0.7%)
Dermatitis exfoliativa	1*(0.9%)	0
Cerebral symptoms	2 (1.8%)	3 (1.1%)
Hemorrhagic encephalopathy	1†	1
Convulsion	1	1
Disorientation	0	1

* Also received sulfanilamide for gonorrhea.
† Death from treatment.

Peripheral neuritis was extremely mild in group 4. For the most part it consisted of paresthesias. There were no significant objective changes. The complication might well have escaped notice but for the astuteness of the examiners in the follow-up clinics.

The lesser toxicity of mapharsen may be due to the smaller arsenic content of the total effectual dose. Whereas neoarsphenamine yields approximately 800 mg. of arsenic in the full dose of 4 Gm., mapharsen contains less than 400 mg. in the 1,200 mg. dose.

Peripheral neuritis was neither prevented nor relieved by vitamin therapy. It bore no relation to the relative excretion of arsenic in urine and stool or to the concentration in the blood. The administration of sodium thiosulfate had no specific therapeutic benefit relative to the neuritis.

G. Nausea and Vomiting: Nausea and vomiting, though not tabulated, were of frequent occurrence, particularly on the first day of treatment. The distress was occasionally severe. No significant metabolic disturbances arose, since the drip furnished adequate amounts of fluid and dextrose.

2. Grave Symptoms (Table 3).—A. Jaundice: The incidence of jaundice was 3.6 per cent with neoarsphenamine and 0.7 per cent with mapharsen. In each instance the jaundice was mild and transitory. There were no symptoms that even remotely suggested the severer forms of toxic hepatitis. Aside from the staining of the tissues and the confirmatory reactions to laboratory tests, no other metabolic phenomena were present. A small number of patients had a transitory elevation of the icteric index without the development of clinical jaundice.

B. Cerebral Symptoms: These were experienced in 1.8 per cent of the neoarsphenamine series and in 1.1 per cent of the mapharsen series. Encephalopathies, although infrequent, were alarming and grave. In 1 instance (the patient was a Negro in the second neoarsphenamine group) the issue was fatal.

Of the patients who had cerebral symptoms, 4 recovered. Besides the Negro who died only 1 man presented a syndrome characteristic of hemorrhagic encephalopathy. Two had a single convulsive seizure and 1 was temporarily disoriented. The recommended remedies, such as sodium thiosulfate and epinephrine, proved of no value.

The most effective therapy consisted of repeated lumbar taps; the continuance of the intravenous infusion with dextrose, sucrose and saline solution, and sedative doses of paraldehyde.

C. Nephropathy: There was no significant nephropathy. Transitory evidences of mild renal irritation (albuminuria, hematuria and cylindruria) were frequently observed.

D. Blood Dyscrasia: One patient with congenital thrombocytopenic purpura was inadvertently treated. No blood dyscrasia developed as the result of therapy.

F. Dermatitis Exfoliativa: One patient had dermatitis exfoliativa. He had received large doses of sulfanilamide for the treatment of acute gonorrhea.

Summary.—Grave complications appeared in 5, or less than 2 per cent, of the 386 patients. The symptoms consisted entirely of cerebral manifestations.

There was 1 death from treatment, a mortality of approximately 0.25 per cent. There were no fatalities with mapharsen.

No delayed or late toxic manifestations have been observed (table 4).

THERAPEUTIC RESULTS

Clinical Material (Table 5).—Four hundred and nine courses of treatment were given to 382 patients. Four men in the second neoarsphenamine group were retreated in the mapharsen series, so that the whole count is 386. Of the 4 patients doubly counted, 3 had definite evidence of reinfection. They are regarded as showing satisfactory results from their primary course of treatment. The fourth patient was previously reported as showing satisfactory results. He later had a fresh penile sore. While there are many data that suggest that he suffered a reinfection, the criteria could not be maintained without reservation. His treatment has therefore been reclassified as a failure in the neoarsphenamine series, but he is included as a new entry in the mapharsen series.

Patients were not refused treatment because of extremes of age. A boy of 13 and a man of 56 are included in the series.

Men with incidental organic disease were not rejected. Patients with pulmonary tuberculosis, rheumatic valvulitis and hypertension were treated without difficulty referable to the therapy or the underlying pathologic condition.

Completion of Treatment Schedule.—With 1 exception, every patient received the amount of drug that was originally ordered. One man, who had slight jaundice on the third day of treatment, was given but 570 of the 1,200 mg. of mapharsen that had been planned.

TABLE 4.—*Complications Conspicuously Absent*

	Neoarsphenamine Series	Mapharsen Series
Nitritoid crises	0	0
Blood dyscrasia	0	0
Nephropathy	0	0
Acute yellow atrophy	0	0

Patients were lost sight of during the course of the follow-up observation, not during the span of active therapy.

Definition of Terms.—The therapeutic results are placed in five categories:

(1) Death from Treatment.

(2) "Loss" of Patient: If a patient failed to report to the follow-up clinic or came but once or twice during

the first three months of observation and was never seen again, he was regarded as lost.

The lost patients received the same amount of therapy as those who were successfully followed. Their chance for a favorable result was not impaired by their absence from the clinic for ambulatory patients. These men received a dose of arsenical sufficient to render them noninfectious to others.

TABLE 5.—*Therapeutic Results (Single Course)*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Total	111	157	118
Death	1	0	0
Loss of patient	13 (11%)	19 (12%)	19 (16%)
Results evaluated	97 (89%)	138 (88%)	99 (84%)

The records of the lost patients are included in the reports of toxicity. They are omitted from the computations of the evaluation of therapy. Efforts to establish contact with these men are still in progress. Should they make a reappearance, they will be reclassified.

In routine ambulatory treatment, the consideration of the lost patients is different. Most ambulatory patients have been inadequately and incompletely treated. They serve as a reservoir of infection. They are more prone to suffer the late ravages of the disease than those who have had no treatment at all. From their ranks are recruited the army of persons with neurosyphilis and the invalids with cardiovascular manifestations.

(3) Unsatisfactory Result: The patients whose treatment was unsatisfactory include those who have had either clinical or serologic evidences of the persistence or relapse of the infection. The treatment of patients in this classification who have been retreated by routine methods is regarded as an irrevocable failure. Those who have been retreated by the intravenous drip method have been reclassified after the second course of treatment.

A definite policy toward retreatment has not yet been formulated. In the neoarsphenamine series, it was decided to stand or fall on a single course. In the small dose mapharsen group, it soon became obvious that the dose of the drug was insufficient. Infectious relapses were encountered. There seemed no valid reason why patients with relapses should not be retreated.

There is no dictum that limits massive dose arsenotherapy to a single course of injections. There is much precedent to justify a repetition of treatment when it is indicated.

When the dose of mapharsen was increased to 1,200 mg. (which seemed to be an optimal safe amount), the incidence of retreatment fell from slightly more than 11 per cent to approximately 5 per cent. Retreatment did not produce any unusual toxicologic phenomena. There were no manifestations of sensitization or cumulation.

An optimum program may include the administration of safe doses to all patients, retreatment being reserved for the few recalcitrant patients inevitably encountered in any clinical therapy.

(4) Pending Result: At this time the results in a few patients cannot be finally classified and are tabulated as pending.

Though the serologic data on these patients are incomplete, there has been no clinical manifestation of syphilis. In a large majority of cases the serologic course has tended strongly toward seroreversal.

Some patients in the early series disappeared after the first three months, before seronegativity was completely achieved. Others, in the later series are still under observation, with considerable promise of a favorable result. The serum of some has appeared clear with one method of testing but not with others.

These patients cannot be classified as lost. The results obtained on them are not unsatisfactory, nor would it be fair to classify them as satisfactory.

In each instance in which examination of the spinal fluid was made the fluid was normal. It is hoped that further reports, at a later date, may permit a more definite classification.

(5) Satisfactory Result: The patient whose treatment is classified as satisfactory has experienced a completely uneventful course. By this is meant that he is clinically well and serologically clear with normal spinal fluid.

The serologic tests include the titered Wassermann technic employed by Mr. John Koopman, the Kolmer titrations as performed by Dr. John Mahoney, the Kahn standard test and the Kline exclusion and diagnostic tests.

The clinical data, in all instances, have been collected by Dr. Evan Thomas or Dr. Bruce Webster at the Bellevue Hospital or the New York Hospital respectively.

The number of negative serologic reactions exceeded ten for most patients. With rare exceptions, the men have had more than six examinations at which the serum has been found normal. Many have had repeated examinations over more than three years.

The reversal of the serologic reaction occurred most commonly between the tenth and the eighteenth week following the completion of therapy.

Some of the patients with seronegative primary syphilis never had positive serologic reactions. In others the reaction became positive after the completion of therapy and then reversed later.

In certain of the patients, particularly those who entered with late secondary syphilis, the reversal of the serologic reaction did not occur for many months.

Needless to say, these patients continue under observation. Since they receive no treatment at the follow-up clinic, their continued presence has been encouraged by paying them a fee of $1 for each visit.

REINFECTION VS. INFECTIOUS RELAPSE

The greatest difficulty in our statistical presentation is the differentiation between reinfection and infectious relapse. Reinfection constitutes a true biologic evidence of "cure." The reinfected patient must be regarded as showing a completely satisfactory result of the previous course of treatment. An infectious relapse must be counted as an irrevocable failure of specific therapy.

Syphilologists have correctly set up rigid standards for the proof of reinfection. These criteria include several technical points that are impossible of fulfilment in the course of massive dose chemotherapy. This discussion will not be pursued further here but will be developed in a later communication.

Reinfection was claimed by 3 patients in the neoarsphenamine series. Each of these men was retreated

with mapharsen. The present courses are eminently satisfactory.

No reinfections were claimed in the mapharsen series, though many clinicians would agree that 8 patients presented evidence that more than strongly suggested a new lesion. Nevertheless, their treatment is reported as a failure so that the statistics may appear in the least favorable light.

Each of these patients has been retreated by the five day method.

TABLE 6.—*Therapeutic Results in Patients Followed (Single Course)*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Number of patients	97	138	99
Unsatisfactory	6 (7%)	24 (18%)	8 (8%)
Pending	4 (4%)	5 (3+%)	9 (9%)
Satisfactory	87 (89%)	109 (79%)	82 (83%)
Recapitulation			
Unsatisfactory		38 (11%)	
Pending		18 (8%)	
Satisfactory		278 (81%)	

STATISTICAL PRESENTATION OF THERAPEUTIC RESULTS

1. *Death from Treatment.*—There was 1 death from treatment, previously described.

2. *Loss of Patient (Table 5).*—Fifty-one patients (13 per cent) were lost to observation. If one subtracts these 51 lost patients and the 1 who died, there remain 334 whose records are sufficiently complete to justify tabulation of the therapeutic results.

3. *Unsatisfactory Result (Single Course of Treatment, Table 6).*—There was an unsatisfactory result from a single course of massive dose arsenotherapy in 38 patients (11 per cent), irrespective of the drug or the dose used.

The patients whose treatment was a failure were reclassified as to (1) infectious relapse, (2) serorelapse and (3) persistently positive reaction of the serum.

1. Twenty-five patients had an infectious relapse. The largest number were in the small dose mapharsen group.

TABLE 7.—*Therapeutic Results (Second Course for Twenty-Three Patients)*

	Mapharsen Group 1	Mapharsen Group 2
Patients retreated	17	6
Result		
Satisfactory after retreatment	12	3
Pending	4	2
Unsatisfactory	1	1

2. Four had a serologic relapse without any clinical manifestation of the disease. Three of these were in the small dose mapharsen group.

3. Nine had a persistently positive reaction of the serum, approaching the condition termed Wassermann fast. Eight were in the small dose mapharsen group. None showed any other clinical evidences of syphilis.

Twenty-three of the patients whose treatment was unsatisfactory were retreated by massive dose chemotherapy. Retreatment of the remaining 15 by routine measures is regarded as an irrevocable failure. It is unfortunate that a policy for treatment was not sufficiently clarified so that these 15 could also have been retreated by the five day method.

4. *Pending Result (Single Course of Treatment, Table 6).*—The results in 18 patients are still pending after a single course of treatment. Half of them have already achieved a seroreversal according to one of the tests. Twelve samples of spinal fluid have been obtained from 11 patients; all were clear. None of the patients has ever shown any clinical evidence of syphilis. The further course of these patients will be reported later.

5. *Satisfactory Result (Single Course of Treatment, Table 6).*—Of the patients in all four groups, without reference to the type of drug or the dosage, 278, or 81 per cent, had a completely satisfactory result from a single experience with massive dose chemotherapy.

THERAPEUTIC RESULTS ANALYZED ACCORDING TO DRUG AND DOSAGE (TABLE 6)

The only patient who died from a complication of treatment was one of the 111 who received neoarsphenamine. There has been no death from treatment among the 275 patients who have received mapharsen.

TABLE 8.—*Recapitulation of Results, Including Revaluation of Those in Twenty-Three Retreated Patients*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Unsatisfactory (irrevocable failure)	6 (7%)	8 (5.8%)	3 (3%)
Pending	4 (4%)	9 (6.6%)	11 (11%)
Satisfactory	87 (89%)	121 (87.6%)	85 (86%)
Recapitulation			
Unsatisfactory		17 (5%)	
Pending		24 (7%)	
Satisfactory		293 (88%)	

The percentage of unsatisfactory results from one course of treatment was 7 in the neoarsphenamine series, 8 in the large dose mapharsen group and 18 in the small dose mapharsen group.

Satisfactory results from a single course were recorded for 89 per cent of the patients given neoarsphenamine, 79 per cent of the small dose mapharsen group (with the result in 3 per cent pending) and 83 per cent of the large dose mapharsen group (with the result in 9 per cent pending).

RETREATMENT IN THE MAPHARSEN SERIES (TABLE 7)

There have been twenty-seven retreatments. Four of the patients were originally in the neoarsphenamine series. They are counted doubly, since they appear also in the mapharsen series.

Twenty-three of the mapharsen series have been retreated with mapharsen. Seventeen were in the small dose group and 6 in the large dose group. The percentage of retreatment has been reduced, by optimal doses, from 11 to approximately 5.

After retreatment, 15 of the mapharsen series may be added to those satisfactorily treated; the results of treatment of 6 are still pending and of 2 are irrevocably unsatisfactory.

RECAPITULATION OF THE MAPHARSEN SERIES AFTER SECONDARY TREATMENT (TABLE 8)

The patients in the mapharsen series who were retreated with mapharsen may be reclassified according to the results following second treatment.

After second courses, the number with unsatisfactory treatment was reduced to 5.8 per cent in the small dose and 3 per cent in the large dose mapharsen group.

TABLE 9.—*Analysis of Irrevocable Failure of Treatment*

	Neoarsphenamine Series	Mapharsep Group 1	Mapharsen Group 2
Infectious relapse	5	6	2
Serorelapse	1	0	0
Persistent seropositivity	0	2	1

Satisfactory results may now be tabulated for 87.6 per cent of the small dose mapharsen group (with the result for 6.6 per cent pending) and 86 per cent of the large dose mapharsen group (with the result for 11 per cent pending). These figures compare favorably with the 89 per cent of satisfactory results with neoarsphenamine.

A recapitulation of the results after the evaluation of the retreatment of patients with mapharsen indicates that 5 per cent of all were unsatisfactory, 7 per cent are still pending and 88 per cent are satisfactory both clinically and serologically.

Irrevocable failure of treatment occurred least often in the second mapharsen group, in which there are but 3 per cent whose course of treatment has been a failure. There are still 11 per cent in this group whose status is pending, and it is more likely that the results in some of these will enter the satisfactory roster than that any patient in whom the results of treatment are satisfactory will evince late manifestations of the infection.

ANALYSIS OF THE IRREVOCABLE FAILURES (TABLE 9)

There were 17 patients whose treatment was an irrevocable failure after primary and secondary courses of treatment. Thirteen of these suffered an infectious relapse. It is conceivable that more than half of these men may well have had a reinfection. Eight were in the small dose mapharsen group. Five of the men in this group received less than 600 mg. One was given

TABLE 10.—*Examinations of Cerebrospinal Fluid*

	Neoarsphenamine Series (111 Patients)	Mapharsen Series
Number of patients examined	80	153
Number of samples of fluid examined	100	167
Normal fluid	99	167
Abnormal fluid	1*	0

* Morphinist with infectious relapse.

700 and 2 approximately 800 mg. The original failure might not have existed had these patients received the optimal dose of 1,200 mg.

Only 1 of those whose treatment was an irrevocable failure had a positive reaction of the spinal fluid. The others presented normal conditions.

Except for the lesion at the site of the original inoculation, no organic manifestation of syphilis was manifested in any of those on whom treatment failed.

The use of an optimal dose of 1,200 mg. of mapharsen, a definitive policy of retreatment and a clearer concept of reinfection might well bring down the percentage of irrevocable failures to an irreducible minimum.

EXAMINATIONS OF CEREBROSPINAL FLUID (TABLE 10)

With few exceptions, each patient has had an examination of the spinal fluid between the sixth and the twelfth month. Many had a second examination after the twenty-fourth month.

In the first neoarsphenamine group, 7 had tests of the spinal fluid after four years. Two hundred and sixty-seven examinations of the spinal fluid have been performed on 233 patients. One patient, a morphinist with a syphilitic wife, has a positive reaction of the spinal fluid. The fluid of the remaining patients is completely normal.

CLINICAL COURSE

The presenting clinical manifestations of syphilis consisted of primary and secondary lesions. During treatment, dark field examination of the primary lesions gave

TABLE 11.—*Seronegative Primary Syphilis*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Number of patients	12	18	16
Lost	..	3	2
Number evaluated	12	15	14
Satisfactory (first treatment)	12 (100%)	13 (86%)	14 (100%)
Unsatisfactory (first treatment)	..	2 (14%)	..
Retreated	..	2	..
Satisfactory after retreatment	..	15 (100%)	..
Unsatisfactory after retreatment	..	..	..

negative results within twenty-four hours or at most forty-eight hours. The secondary eruptions rapidly faded.

Physical examinations were made in the follow-up clinics by Dr. Thomas and Dr. Webster and their staffs. Thus far, no visceral manifestation of syphilis has been encountered in any patient, other than the infectious relapse at the site of the original inoculation.

There has been no clinical evidence, as yet, of syphilis of the central nervous system or the cardiovascular system.

The first group treated with neoarsphenamine was observed after five years. Many patients in the second group are in the fourth year of observation.

RESULTS IN SERONEGATIVE PRIMARY SYPHILIS (TABLE 11)

Forty-six (12 per cent) patients were admitted in the seronegative primary phase of the disease. Twelve were treated with neoarsphenamine and 34 with mapharsen. Eighteen of the 34 received the small doses of mapharsen, varying from 0.5 to 1 Gm., while the remaining 16 received the optimal dose of 1.2 Gm.

Of the patients with seronegative primary syphilis, 22 never had a significant increase in the serologic reaction. The remaining patients became seropositive on discharge. Forty-one were observed for a sufficient length of time for treatment to be evaluated. Thirty-nine (95 per cent) pursued a wholly satisfactory and uneventful course. Two had fresh lesions on the penis.

with mapharsen. The present courses are eminently satisfactory.

No reinfections were claimed in the mapharsen series, though many clinicians would agree that 8 patients presented evidence that more than strongly suggested a new lesion. Nevertheless, their treatment is reported as a failure so that the statistics may appear in the least favorable light.

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5. *Satisfactory Result (Single Course of Treatment, Table 6).*—Of the patients in all four groups, without reference to the type of drug or the dosage, 278, or 81 per cent, had a completely satisfactory result from a single experience with massive dose chemotherapy.

THERAPEUTIC RESULTS ANALYZED ACCORDING TO DRUG AND DOSAGE (TABLE 6)

The only patient who died from a complication of treatment was one of the 111 who received neoarsphenamine. There has been no death from treatment among the 275 patients who have received mapharsen.

TABLE 8.—*Recapitulation of Results, Including Revaluation of Those in Twenty-Three Retreated Patients*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Unsatisfactory (irrevocable failure)	6 (7%)	8 (5.8%)	3 (3%)
Pending	4 (4%)	9 (6.6%)	11 (11%)
Satisfactory	87 (89%)	121 (87.6%)	85 (86%)
Recapitulation			
Unsatisfactory		17 (5%)	
Pending		24 (7%)	
Satisfactory		293 (88%)	

The percentage of unsatisfactory results from one course of treatment was 7 in the neoarsphenamine series, 8 in the large dose mapharsen group and 18 in the small dose mapharsen group.

Satisfactory results from a single course were recorded for 89 per cent of the patients given neoarsphenamine, 79 per cent of the small dose mapharsen group (with the result in 3 per cent pending) and 83 per cent of the large dose mapharsen group (with the result in 9 per cent pending).

RETREATMENT IN THE MAPHARSEN SERIES (TABLE 7)

There have been twenty-seven retreatments. Four of the patients were originally in the neoarsphenamine series. They are counted doubly, since they appear also in the mapharsen series.

Twenty-three of the mapharsen series have been retreated with mapharsen. Seventeen were in the small dose group and 6 in the large dose group. The percentage of retreatment has been reduced, by optimal doses, from 11 to approximately 5.

After retreatment, 15 of the mapharsen series may be added to those satisfactorily treated; the results of treatment of 6 are still pending and of 2 are irrevocably unsatisfactory.

RECAPITULATION OF THE MAPHARSEN SERIES AFTER SECONDARY TREATMENT (TABLE 8)

The patients in the mapharsen series who were retreated with mapharsen may be reclassified according to the results following second treatment.

After second courses, the number with unsatisfactory treatment was reduced to 5.8 per cent in the small dose and 3 per cent in the large dose mapharsen group.

TABLE 9.—*Analysis of Irrevocable Failure of Treatment*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Infectious relapse	5	6	2
Serorelapse	1	0	0
Persistent seropositivity	0	2	1

Satisfactory results may now be tabulated for 87.6 per cent of the small dose mapharsen group (with the result for 6.6 per cent pending) and 86 per cent of the large dose mapharsen group (with the result for 11 per cent pending). These figures compare favorably with the 89 per cent of satisfactory results with neoarsphenamine.

A recapitulation of the results after the evaluation of the retreatment of patients with mapharsen indicates that 5 per cent of all were unsatisfactory, 7 per cent are still pending and 88 per cent are satisfactory both clinically and serologically.

Irrevocable failure of treatment occurred least often in the second mapharsen group, in which there are but 3 per cent whose course of treatment has been a failure. There are still 11 per cent in this group whose status is pending, and it is more likely that the results in some of these will enter the satisfactory roster than that any patient in whom the results of treatment are satisfactory will evince late manifestations of the infection.

ANALYSIS OF THE IRREVOCABLE FAILURES (TABLE 9)

There were 17 patients whose treatment was an irrevocable failure after primary and secondary courses of treatment. Thirteen of these suffered an infectious relapse. It is conceivable that more than half of these men may well have had a reinfection. Eight were in the small dose mapharsen group. Five of the men in this group received less than 600 mg. One was given

TABLE 10.—*Examinations of Cerebrospinal Fluid*

	Neoarsphenamine Series (111 Patients)	Mapharsen Series
Number of patients examined	80	153
Number of samples of fluid examined	100	167
Normal fluid	99	167
Abnormal fluid	1*	0

* Morphinist with infectious relapse.

700 and 2 approximately 800 mg. The original failure might not have existed had these patients received the optimal dose of 1,200 mg.

Only 1 of those whose treatment was an irrevocable failure had a positive reaction of the spinal fluid. The others presented normal conditions.

Except for the lesion at the site of the original inoculation, no organic manifestation of syphilis was manifested in any of those on whom treatment failed.

The use of an optimal dose of 1,200 mg. of mapharsen, a definitive policy of retreatment and a clearer concept of reinfection might well bring down the percentage of irrevocable failures to an irreducible minimum.

EXAMINATIONS OF CEREBROSPINAL FLUID (TABLE 10)

With few exceptions, each patient has had an examination of the spinal fluid between the sixth and the twelfth month. Many had a second examination after the twenty-fourth month.

In the first neoarsphenamine group, 7 had tests of the spinal fluid after four years. Two hundred and sixty-seven examinations of the spinal fluid have been performed on 233 patients. One patient, a morphinist with a syphilitic wife, has a positive reaction of the spinal fluid. The fluid of the remaining patients is completely normal.

CLINICAL COURSE

The presenting clinical manifestations of syphilis consisted of primary and secondary lesions. During treatment, dark field examination of the primary lesions gave

TABLE 11.—*Seronegative Primary Syphilis*

	Neoarsphenamine Series	Mapharsen Group 1	Mapharsen Group 2
Number of patients	12	18	16
Lost	..	3	2
Number evaluated	12	15	14
Satisfactory (first treatment)	12 (100%)	13 (86%)	14 (100%)
Unsatisfactory (first treatment)	..	2 (14%)	..
Retreated	..	2	..
Satisfactory after retreatment	..	15 (100%)	..
Unsatisfactory after retreatment	..	..	..

negative results within twenty-four hours or at most forty-eight hours. The secondary eruptions rapidly faded.

Physical examinations were made in the follow-up clinics by Dr. Thomas and Dr. Webster and their staffs. Thus far, no visceral manifestation of syphilis has been encountered in any patient, other than the infectious relapse at the site of the original inoculation.

There has been no clinical evidence, as yet, of syphilis of the central nervous system or the cardiovascular system.

The first group treated with neoarsphenamine was observed after five years. Many patients in the second group are in the fourth year of observation.

RESULTS IN SERONEGATIVE PRIMARY SYPHILIS (TABLE 11)

Forty-six (12 per cent) patients were admitted in the seronegative primary phase of the disease. Twelve were treated with neoarsphenamine and 34 with mapharsen. Eighteen of the 34 received the small doses of mapharsen, varying from 0.5 to 1 Gm., while the remaining 16 received the optimal dose of 1.2 Gm.

Of the patients with seronegative primary syphilis, 22 never had a significant increase in the serologic reaction. The remaining patients became seropositive on discharge. Forty-one were observed for a sufficient length of time for treatment to be evaluated. Thirty-nine (95 per cent) pursued a wholly satisfactory and uneventful course. Two had fresh lesions on the penis.

There was strong presumptive evidence that both of these had suffered a reinfection. One had received but 600 mg. of mapharsen and the other 800 mg. Both men were regarded as showing unsatisfactory results and were retreated with mapharsen. The results in both are now completely satisfactory.

The total of satisfactory results after the original and the second courses of treatment of seronegative primary syphilis was 100 per cent.

SUMMARY

1. In a series of 382 cases of early syphilis, involving massive dose chemotherapy by the intravenous drip method with neoarsphenamine and mapharsen, there was 1 death from treatment (0.25 per cent). No deaths occurred with mapharsen.

2. The minor and annoying toxicologic phenomena included local reactions, primary and secondary fever, toxicodermas, nausea and vomiting. There was significantly less disturbance in the mapharsen series.

3. Of the moderately severe toxic symptoms, peripheral neuritis, which occurred in more than one third of the patients who received neoarsphenamine, was reduced to a negligible incidence of mild paresthesia in the mapharsen series.

4. Of the grave untoward phenomena associated with arsenotherapy, only the cerebral symptoms were encountered. These were experienced in 1.8 per cent of the neoarsphenamine series and in 1.1 per cent of the mapharsen series. The encephalopathy accounted for the 1 death from treatment, which occurred after the administration of neoarsphenamine.

5. From the therapeutic standpoint, the statistics are presented in their least favorable light. Eight possible reinfections are regarded as infectious relapses. Results in patients who are clinically well but serologically positive (S T S) are classified as unsatisfactory.

6. Taking the series as a unity, without reference to the type of drug or the dosage, and classifying as unfavorable all questionable results, we find that 81 per cent of the patients had a completely satisfactory course, even when we employ the most rigid clinical and laboratory indexes.

7. Including favorable results from retreatment in an additional 15 cases, the total number of satisfactory results approximates 88 per cent for the entire series.

8. With a single exception, the spinal fluid of every patient has become completely clear.

9. With the exception of the infectious relapse at the site of the original inoculation, no organic manifestation of syphilis has yet been noted. Here the reservation is entered that many patients have been but recently observed. However, the patients of series 1 were reexamined at the end of five years, and many of the patients of series 2 have passed three years of observation.

10. The irrevocable failures approximate 5 per cent. A definitive policy for retreatment might have appreciably lowered this precentage.

11. The treatment of none of the 41 patients with seronegative primary syphilis, 2 of whom were retreated with massive dose arsenotherapy, was a failure, 100 per cent of the results being satisfactory.

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AN EVALUATION OF THE MASSIVE DOSE THERAPY OF EARLY SYPHILIS

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Ehrlich first attempted to cure syphilis with massive doses of arsphenamine, but because of unsatisfactory results the use of massive arsenotherapy was replaced by multiple injection plans with the interim administration of heavy metals. These methods require uninterrupted therapy over a long period of time. In 1933 Chargin, Leifer and Hyman, using the method of slow intravenous drip, again revived the massive dose procedure. Within a period of five days these workers administered from 4 to 4.5 Gm. of neoarsphenamine. In 1938 the frequency of untoward reactions with neoarsphenamine, especially the appearance of peripheral neuritis, persuaded them to substitute an arsenoxide in preference to neoarsphenamine.

In view of the degree of success indicated by the initial results reported by the New York group, it seemed advisable to extend the work in order to make further evaluation of the hazards and effectiveness of this new treatment scheme. A plan was evolved for pooling correlated information from several hospitals in order that a larger number of cases might be brought into the study within a shorter time than could possibly be obtained from any one clinic working alone. This paper is a progress report on the results and observations of arsenoxide therapy in cases of early syphilis under this method in the following hospitals:

Mount Sinai Hospital, New York.
Bellevue Hospital, New York.
Long Island College Hospital, New York.
New York Hospital, New York.
Herman Kiefer Hospital, Detroit.
Receiving Hospital, Detroit.
Cook County Hospital, Chicago.
City Hospital, Indianapolis.
Wisconsin General Hospital, Madison.
University Hospital, Minneapolis.
Broadlawns Hospital, Des Moines, Iowa
Isolation Hospital, St. Louis.
City Hospital, Cleveland.

Answers to the following questions were sought:

1. What is the treatment fatality rate?

2. What kinds of nonfatal reactions to treatment were observed and how frequently did they occur?

3. What was the serologic response in the cases so treated?

4. What proportion of the patients after a single course of massive dose therapy may be expected subsequently to show evidence of failure to achieve cure?

Read before the Section on Dermatology and Syphilology at the Ninety-Second Session of the American Medical Association, Cleveland, June 5, 1941.

POPULATION AND METHODS

Nine hundred and sixty-eight cases of primary and secondary syphilis not complicated by pregnancy are included in this study. In some of the cases one or two injections of an arsenical were administered prior to hospital admission, but in the main these cases represent untreated cases of early syphilis. The diagnosis was confirmed by dark field and blood examination. The uniformity of the serologic interpretations was enhanced by the fact that a large majority were performed in either the University of Michigan laboratory or the U. S. Public Health Service Venereal Disease Research Laboratory. Both laboratories employed the Kahn test. The total amount of arsenoxide administered in the treatment varied from 250 to 1,250 mg., with 1,200 mg. as the amount most frequently used. Recent experimental work [1] suggests that 1,200 mg. of arsenoxide in five days, in a 60 Kg. man, corresponds to 40 per cent of the maximum tolerated dose in dogs.

Three different injection schedules for administering the arsenical were employed in the treatment of these cases, as follows:

(*a*) *Slow Intravenous Drip.*—This consisted of a continuous injection of 2,000 cc. of solution during a period of seven to ten hours daily.

(*b*) *Rapid Intravenous Drip.*—This consisted of a continuous injection of approximately 1,000 cc. of solution during a period of approximately one to not more than three hours daily.

TABLE 1.—*Distribution by Admission Diagnosis of 968 Cases Studied*

Diagnosis	Number	Per Cent
Seronegative primary	125	12.9
Seropositive primary	268	27.7
Secondary	575	59.4
Total	968	100.0

(*c*) *Multiple Injection Method.*—This consisted of one or more rapid injections by syringe technic of small amounts of solution daily.

Since there are not enough cases in each of these three groups to permit us to make a comparison of the relative values of these hospital practices, our report will classify patients according to diagnosis, total dosage of drug received and length of observation.

During the hospital period patients were observed closely for reactions; urine and blood studies were performed frequently and other special tests as indicated. At each follow-up visit the patients were questioned carefully concerning their current history, the skin and mucous membranes were minutely inspected and a serologic test for syphilis was performed. When suggestive lesions were found, darkfield examinations were made. When possible, spinal fluid examinations were made six months to one year following treatment.

In table 1 is given the distribution of the 968 cases by admission diagnosis. Thirteen per cent were seronegative primary cases, 28 per cent were seropositive primary and 59 per cent were in the secondary stage of the disease. Of these patients 699, or 72 per cent, were males.

The cooperating hospitals were divided into two groups according to the length of time they have been using massive dose therapy, and their patients are designated series 1 and series 2 respectively. From table 2 it can be seen that the patients in series 1 as a whole have been observed for a longer time than those of series 2. For example, 75 per cent of the patients in series 1 were observed in the interval six months to one year, whereas only 52 per cent of those in series 2 were observed for the same length of time. Beyond this period the difference between the number of patients seen in the two series is more pronounced. The study of serologic response and of treatment failures has been confined to series 1. It is recognized that the value of our analysis of serologic response and of treatment failures is limited by the short period of post-treatment observation and it should be emphasized that this paper is only a report of progress.

TABLE 2.—*Length of Post-Treatment Observation of 968 Cases*

Period	Series 1 Cases Held to Period		Series 2 Cases Held to Period	
	Number	Per Cent	Number	Per Cent
Total cases	502	100.0	466	100.0
Discharge-1 month	499	99.4	452	97.0
1-2 months	442	88.0	414	88.8
2-3 months	419	83.5	366	78.5
3-6 months	396	78.9	297	63.7
6 months-1 year	376	74.9	243	52.1
1-2 years	285	56.8	89	19.1
2-3 years	135	26.9	13	2.8
3-4 years	23	4.6	..	...

Note: These patients are not necessarily lost from future observation.

RESULTS

Reactions to Treatment.—Patients in both series were used for the study of treatment reactions. With the exception of a few cases of delayed mild peripheral neuritis, all of the reactions to treatment which were observed occurred either during or within two to three days after the completion of treatment. We believe that our observations with respect to this phase of the problem are adequate.

TABLE 3.—*Percentage of Total Patients Exhibiting Specified Treatment Reactions*

Reaction	Series 1, 502 Cases			Series 2, 466 Cases		
	Under 1,150 Mg.	1,150 Mg. or Over	Total	Under 1,150 Mg.	1,150 Mg. or Over	Total
Reactive cases	95.2	96.0	95.5	86.8	94.2	91.2
Primary fever	62.9	45.6	55.7	15.3	55.8	39.3
Secondary fever	53.7	61.4	56.9	13.7	31.2	24.0
Toxicodermas	11.9	16.8	13.9	5.8	10.5	8.6
Pain in arm	30.9	36.5	33.2	24.7	66.3	49.4
Nausea	43.2	63.8	51.7	72.1	64.9	67.8
Renal damage	0.7	....	0.4	0.5	0.7	0.6
Liver damage	7.1	11.0	8.8	18.4	4.0	9.9
Neuritis, motor	0.7	0.5	0.6	0.5	0.4	0.4
Sensory only	0.1	8.2	7.0	2.1	6.2	4.5
Unspecified	1.0	1.4	1.2	0.5	3.3	2.1
Cerebral, mild	45.2	27.8	38.0	15.3	28.6	23.2
Serious: Fatal	0.3	...	0.2	...	0.7	0.4
Nonfatal	0.7	0.5	0.6	...	0.7	0.4
Other	5.1	5.3	5.2	3.2	2.9	3.0
None	4.8	3.8	4.4	13.2	5.8	8.8

For estimating the fatality experience, all of our own patients, together with all available reported cases, were considered. A total of 1,600 patients have come to our attention as receiving massive dose therapy, and 5 treatment deaths have been reported. This constitutes a fatality rate of 0.3 per cent, which is represented graphically in figure 1. These patients presented a

1. Magnuson, H. J.; Raulston, B. O., and Muff, Anthony: Ven. Dis. Inform. **22**: 157 (May) 1941.

clinical picture of hemorrhagic encephalitis beginning with mental confusion and followed by convulsions, coma and death.

In one autopsy report the microscopic examinations of brain and spinal cord tissue showed areas of early focal demyelination. "This process appears to be secondary to some injurious agent, the exact nature of which cannot be determined by the microscopic examination. The petechiae and hyaline thrombi so often seen in arsenic encephalitis are not encountered." Conclusion: 1. Encephalopathy (secondary possibly to arsenic—clinical).

In a second autopsy report the anatomic diagnoses are as follows:

1. Syphilis, secondary (roseola syphilitica).
2. Mapharsen poisoning (clinical).
3. Edema—brain.
4. Cloudy swelling—viscera.
5. Tracheobronchitis, acute.
6. Congestion—lungs.
7. Malaria, obsolete.

In the third case the report on the gross section of the brain is as follows:

Superficial examination reveals no evident lesions of blood vessels, leptomeninx or brain, other than congestion.

After microscopic examination a final diagnosis is given as petechial hemorrhages in the twelfth nucleus; cerebral congestion and edema.

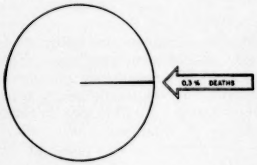

Fig. 1.—Treatment fatalites in 1,600 cases treated.

These three autopsies have failed to confirm the clinical impression of hemorrhagic encephalitis or reveal any definite findings which would allow a clearcut pathologic diagnosis to be made.

Sometime during the treatment period from 90 to 95 per cent of the patients experienced some reaction. Most of the complaints were mild and seldom necessitated the interruption of the scheduled treatment. As shown in table 3, these were more frequent when the total dosage of arsenoxide was greater than 1,150 mg. The six most common complaints and reactions in the order of their frequency (both series and all doses) were:

1. Nausea, 60 per cent.
2. Primary fever (fever on the first day), 48 per cent.
3. Secondary fever (fever occurring on any subsequent day), 41 per cent.
4. Pain in the arm, 41 per cent.
5. Cerebral symptoms (mainly headache), 31 per cent.
6. Toxicodermas, 11 per cent.

Noteworthy was the low incidence of kidney irritation, impairment of liver function and peripheral neuritis. Cases reported as impairment of liver function were so classified when the icteric index was greater than 10. This occurred in 9 per cent of the cases but usually returned to normal during the course of treatment. Only 2 cases of clinical jaundice were seen. The observed peripheral neuritis was transient and mild. There was a complete absence of dermatitis exfoliativa, blood dyscrasia and nitritoid reactions.

SEROLOGIC RESULTS

Table 4 portrays the serologic response of patients in series 1. This is presented by admission diagnosis at three points in time following treatment, namely on the completion of treatment, at the intervals two to three months, and six months to one year. The number

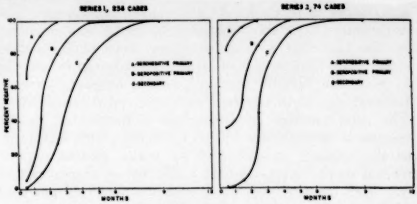

Fig. 2.—Rate at which sustained negative cases attained that status.

of negative blood tests obtained has been related to the number of cases actually observed within each time interval.

From the table it is seen that about 60 per cent of the seronegative primary cases were still negative on completion of treatment. Conversely, it is apparent that in 40 per cent of these cases a transient upsurge into the positive zone was noticed, but 97 per cent of the seronegative primary cases observed were negative in the two to three month period. Seventy-seven per cent of the seropositive primary cases were seronegative at two to three months, but of those observed at six months to one year 85 per cent were negative. At two to three months the secondary cases showed only 36 per cent seronegative—only half as many as were obtained on the seropositive primary cases in this time interval. By six months to one year, however, nearly 80 per cent were seronegative.

Table 5 and figure 2 indicate the rate at which sustained seronegative cases in series 1 and 2 respectively attained that status. A sustained seronegative case was defined as one which exhibits two successive negative blood tests and which yields no positive test within two months after the first negative test was observed.

In the period immediately following treatment negative blood tests were exhibited by only 66 per cent of

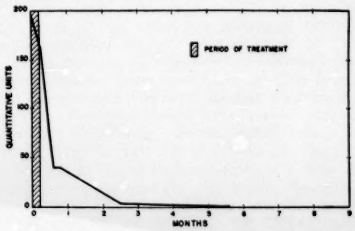

Fig. 3.—Typical quantitative serologic curve in a seropositive case.

the originally seronegative primary cases of series 1 and by 81 per cent of series 2. It may be seen that all of those seronegative primary cases which have been observed to satisfy the criteria of sustained seronegativity had attained that status by the end of two or three months, whereas all the seropositive primary

cases attained this status within about six months, and all the secondary cases in this category within about one year.

Figure 3 illustrates a typical curve of quantitative serologic titers in a seropositive primary case. It is anticipated that the results of such quantitative serologic studies will be reported in a separate communication.

TREATMENT FAILURES

Patients who had completed one course of massive dose therapy were considered treatment failures if, thereafter, they exhibited mucocutaneous relapse, were seroresistant for one year, suffered serorelapse or gave other evidence of progression or resistance of the disease. Spinal fluid examinations were performed within the first year on 263 of the 441 patients studied for evidences of treatment failure, the majority of these being performed in the interval six months to one year. Five positive spinal fluids were observed.

In the interest of conservatism all cases reported as probable reinfections were classified as mucocutaneous relapses and, therefore, as treatment failures. If these patients can actually be shown to have acquired reinfections, the rates of failure presented in the next table should be revised downward. Some of the cases which failed after one course of treatment were subjected to massive dose therapy a second time, and some of these gave evidence of a satisfactory outcome. In this study, however, only the results of the first course of therapy are included.

TABLE 4.—*Series 1: Results of Blood Serologic Tests by Admission Diagnosis*

		Completion of Treatment			Two to Three Months			Six Months to One Year		
			Negative			Negative			Negative	
	Cases Treated	Total	Number	Per Cent	Total	Number	Per Cent	Total	Number	Per Cent
Seronegative primary	56	54	31	57.4	40	39	97.5	29	28	96.6
Seropositive primary	130	127	3	2.4	90	69	76.7	78	66	84.6
Secondary	316	306	2	0.7	181	65	35.9	169	134	79.3

Since the length of observation is an essential factor in the determination of the rate of treatment failure, this portion of the study was limited to 441 cases within series 1 which had the longer observation period. It was further limited to the observation periods up to six months to one year, since beyond this period the number of cases observed was small. The observed rate of failure in each time interval was applied to a residuum of the original group of cases in order to estimate the number of failures which would have occurred had all cases been observed in all time intervals up to and including the six months to one year period. This procedure provided an expected rate failure on the basis of 1,000 cases treated, as presented in table 6. Uniformly the expected rate of failure was greater among the patients who received less than 1,150 mg. of arsenoxide than among those who received a higher dosage. Although the individual differences are not statistically significant, the fact that all of them are in the same direction indicates that the differences are probably real. Furthermore, the highest rate of failure among the high dosage cases was lower than the lowest rate of failure among the low dosage group. These observations suggest that the larger doses are more effective in preventing treatment failures. One year's observations indicate that one may expect a single course of massive dose therapy, using 1,200 mg. of arsenoxide, to be unsuccessful in from 5 to 15 per cent of patients with early syphilis.

TABLE 5.—*Series 1: Time at Which 256* Sustained Seronegative Cases First Attained That Status*

	Seronegative Primary		Seropositive Primary		Secondary	
Period	Cases	Cumulative Percentage of Total	Cases	Cumulative Percentage of Total	Cases	Cumulative Percentage of Total
All cases	44	100.0	75	100.0	137	100.0
Admission-1 month	29	65.9	4	5.3	..	0.0
1-2 months	11	90.9	27	41.3	12	8.8
2-3 months	4	100.0	29	80.0	25	27.0
3-6 months	..	.....	14	98.7	69	77.4
6 months-1 year	..	.....	1	100.0	30	99.3
1-2 years	..	.....	..	.....	1	100.0

Series 2: Time at Which 74† Sustained Seronegative Cases First Attained That Status

All cases	27	100.0	20	100.0	27	100.0
Admission-1 month	22	81.5	7	35.0	0	0.0
1-2 months	4	96.3	3	50.0	1	3.7
2-3 months	1	100.0	7	85.0	11	44.4
3-6 months	..	.....	3	100.0	13	92.6
6 months-1 year	..	.....	..	.....	2	100.0

* Among 502 cases treated. † Among 466 cases treated.

SUMMARY

Massive arsenotherapy by means of the five day intravenous drip of an arsenoxide, or one of several modifications, has been employed on about 1,600 patients. In order to determine the therapeutic effectiveness of the method, a detailed study was made of the case records of 968 of these patients with early syphilis treated and observed in thirteen hospitals. Although the period of observation is still too brief to permit final evaluation, the clinical and serologic trend indicates that the percentage of therapeutic failures occurring within six months to one year after a single course of massive dose therapy will probably be between 5 and 15 per cent when 1,200 mg. of arsenoxide is used.

Five deaths occurred among the 1,600 treated patients, presumably from toxic encephalitis, a fatality rate of 0.3 per cent. Among the 968 cases intensively studied, other toxicologic manifestations were mild and seldom interfered with the treatment schedule. There was little evidence of liver damage and no significant renal damage; peripheral neuritis, when it was detected, was transient and mild; neither dermatitis exfoliativa, blood dyscrasias nor nitritoid reactions were observed.

TABLE 6.—*Series 1: Expected Rate per Thousand of Treatment Failure Through the Interval Six Months to One Year*

	Total Dose		
Diagnosis	Under 1,150 mg.	1,150 mg. or Over	All Doses
Seronegative primary	171	45	115
Seropositive primary	147	128	139
Secondary	223	105	174
All diagnoses	180	93	139

CONCLUSION

This work is presented as a progress report. Observations on the patients studied will continue.

The public health importance of a method which offers the possibility of eliminating the infection in at least 85 per cent of the early cases of syphilis with five successive days of treatment and presents an opportunity for the rapid control of this disease warrants the continuation of the present study in well organized treatment centers.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. LEIFER, CHARGIN AND HYMAN AND DRS. ELLIOTT, BAEHR, SHAFFER, USHER AND LOUGH

DR. EVAN W. THOMAS, New York: Another year's follow-up of cases of early syphilis in which massive arsenotherapy has been employed by the intravenous drip method of Leifer, Chargin and Hyman has added to the significance of the pioneer efforts of these investigators. Now, thanks to the efforts of the United States Public Health Service, we have a valuable statistical review of the more important massive arsenotherapy experiments undertaken in this country. More time must elapse before the data can be properly evaluated, but certain features seem worthy of emphasis at this time: 1. In mapharsen we have an arsenical drug which can be given with a minimum of toxic effects. There is little question that in massive dosage the use of mapharsen permits experiments which would not be practical in the case of other arsphenamines. 2. There seems to be increasing evidence that the quick treatment of early syphilis is possible without resorting to a continuous intravenous drip. 3. Blood arsenic levels determined at Bellevue Hospital during and after treatment with divided doses of mapharsen roughly paralleled those reported at Mount Sinai Hospital, where the drug was given by the intravenous drip. 4. The incidence of cerebral symptoms has been about 1 per cent in all the quick methods of treatment. This is appreciably greater than has ever been recorded with routine therapy. It presents a serious problem demanding further study. In the hope of preventing cerebral symptoms, at Bellevue Hospital we have used a combination of fever and mapharsen in 212 cases. Fevers have been induced by typhoid vaccines intravenously and the total dosage of mapharsen has been under 1 Gm. in all cases. 5. Therapeutically the results of none of the attempts at the quick cure of early syphilis represent a panacea, but they compare favorably with the published statistics of cases which have been followed for a similar period of time with good routine therapy. Most encouraging from a therapeutic point of view is the fact that spinal fluids examined from six to twenty-four months after the completion of treatment have been negative in practically every instance, except where infectious relapses have been recorded. 6. Apart from the incidence of encephalitis, one of the chief objections to further experimentation with massive arsenotherapy has been the necessity of hospitalizing patients. It seems to me, however, that the advantages of hospitalizing all persons with early infectious syphilis far outweigh those of treating the patients in hurried clinics.

DR. HERBERT RATTNER, Chicago: At the Cook County Hospital we have used this method of treatment for 180 patiente with early syphilis, 70 of them women. We administered 1,200 mg. of mapharsen regardless of weight or sex. The first patient was treated in August 1940, so that the time is too short to permit conclusions. But it is important to note that our early findings with respect to reactions and clinical results seem to run a curve that parallels exactly that of the early findings of the New York group. There have been but two cases with serious reactions. One man after treatment on the third day suffered a single convulsion which left no sequelae. Another man on the sixth day had several convulsions, became comatose and then suffered a hemiplegia. He too recovered with no sequelae. The blood reactions of both patients became negative and were still negative six months later. We have not encountered a single instance of exfoliative dermatitis or of blood dyscrasias, nor has there been a single case of renal or hepatic damage and, of course, no nitritoid reactions. The clinical results in the first 80 cases, treated more than five months ago, show that we too are having difficulty in determining whether some cases represent relapses, reinfections or superinfections. The blood reactions of a woman whom we treated for secondary syphilis became negative and remained so for three months. Then she reported with a chancre on her lip and insisted that she had never before had a sore on her lip. We look on this case as one of reinfection. There were three other cases which, for reasons of the sort, we also think are examples of reinfection or superinfection. Four patients have suffered relapses. Among our patients were 5 pregnant women with early syphilis. Two, in their seventh month of pregnancy, reported with eruptions of secondary syphilis. They both have given birth to apparently normal babies, the older one now 14 weeks of age. We have since treated a woman in the fourth month of pregnancy and another in the second month without any untoward effects on the pregnancy. They are both awaiting delivery.

DR. GEORGE BAEHR, New York: I have had the privilege of observing the work of Drs. Leifer, Chargin and Hyman for almost eight years, because it was carried out in my service at Mount Sinai Hospital. I have also had the privilege of analyzing with the Public Health Service the observations which have been made during the past year in twelve other hospitals. In spite of the encouragement which these observations offer, I should like to speak a word of caution on behalf of all the observers who have participated in this work. The technic should not be released to the general profession at present, not until a still wider hospital experience has been gained. On the other hand, I do not think that any well organized treatment center need hesitate to try out the method under the same conditions with which it has now been employed in many hospitals throughout the country. Until a much larger volume of experience is gained and observations have been made which will reduce the possible hazard of so-called arsenical encephalitis, the treatment should be restricted to well organized hospitals. The great public health significance of this work is apparent, I am sure. I think the time has come when we must reorient our point of view concerning the measures necessary for the control of syphilis. We must approach the problem of syphilis control as we do the control of other communicable diseases. In our attempts to control tuberculosis during the past thirty-five years we have stopped at nothing, including the provision of tens of thousands of hospital beds, without counting the cost. Although the five day drip therapy for the early highly communicable stage of syphilis requires hospitalization, why count the small cost compared with tuberculosis if a week of hospital care will prevent 85 to 90 per cent thereafter from communicating their disease to others? Thirty years' experience with conventional therapy still leaves us with hundreds of thousands of new cases annually. The technic as described here today provides the means for the rapid eradication of one of the most widespread communicable diseases of mankind.

DR. W. F. SPILLER, Galveston, Texas: I have treated practically 70 cases in Galveston. I regret to have to report one fatality, from acute encephalitis. That is the only severe reaction which occurred. However, when patients start to show much of a reaction, I discontinue the treatment, which has been seldom. Few cases have had to be discontinued. A young white woman, started with the treatment in September, had to discontinue treatment on account of nausea and vomiting. In December she resumed treatment again and went on through her five days of treatment without any untoward results. In January her blood was normal and it has remained normal. A young Negro came in with a secondary eruption and went through his treatment without any reaction. He completed the treatment the latter part of March. Just one week ago he came to the clinic with a typical hunterian chancre, positive dark field, which I regarded as a recurrence, which could be a reinfection. One modification that I am making in this treatment is after the five day drip treatment I continue giving soluble bismuth three times a week for about eight to ten weeks. The most

frequently occurring reactions are nausea, vomiting and arm pain. The nausea and vomiting occur on the first day. It may be quite a bit psychologic because if one gets the patient to go on and try to continue the treatment, the next day, as a rule, he does not have any trouble. I have found that, if the rate of drip is stepped up, as a rule the arm pains will get less or disappear.

DR. MAURICE J. STRAUSS, New Haven, Conn.: For many years I have been concerned with the public health aspect of syphilis in New Haven. I have been interested in this method because the results are at least as good as those with the standard methods of treatment; second, the patient is hospitalized during the infectious period, and, third, all or almost all of the patients can complete their course of treatment. This question of the patients not finishing treatment, the so-called case loss, is one of the most discouraging factors in the control of early syphilis. We are fortunate in having in New Haven a hospital equipped to carry out this form of treatment. For the past eighteen months we have sent to the hospital every patient with early syphilis who has come to any clinic or hospital in New Haven. I might add that this represents practically all the cases occurring in New Haven. And of these patients, every one has completed what is considered a satisfactory course of treatment. That is something which cannot be said for any similar period previous to this time. I only want to add that the New Haven health department has spent quite a lot of money on this. We have paid for the hospitalization of almost all the patients in the small series done in New Haven, and we feel it has been a very good investment.

DR. JOSEPH F. SADUSK JR., New Haven, Conn.: Since January 1940 the five day therapy has been employed at the New Haven Hospital on an experimental basis for the treatment of 13 cases of primary or secondary syphilis. The drug used was mapharsen, the dosage 1,200 mg. and the technic similar in every respect to that outlined by the Mount Sinai group. The New Haven Department of Health, through the courtesy of Dr. Strauss, has cooperated with us at the Yale University School of Medicine in carrying out this treatment. These few cases have been followed for periods varying from two months to one and one-half years, and it is evident, therefore, that I can offer but little in addition to what has already been said about this mode of therapy. What I should like to point out, however, is that this method of treatment can be satisfactorily employed on a small scale. Twelve of the 13 patients have had a complete seroreversal, ranging in time from three to twenty-five weeks following therapy. The 1 patient who has not yet had a seroreversal has been followed for only thirteen weeks. One patient followed now for one and one-half years became pregnant four weeks after therapy and received no further antisyphilitic therapy, since she had a complete seroreversal about eight weeks after therapy. Six months ago she delivered a normal, full term child in the New Haven Hospital. This child up to date shows no serologic, roentgen ray or clinical evidence of syphilis. On the last few patients treated we have been doing lumbar punctures immediately at the completion of the therapy. In one instance of seropositive primary syphilis the Wassermann reaction in the spinal fluid was strongly positive and there was a positive colloidal gold curve. Four weeks later the serologic reaction was negative and the colloidal gold curve was negative. The toxic reactions that we have observed are essentially similar to those just outlined, but we have had no manifestations of cerebral toxicity. Approximately one half of our patients developed a mild secondary anemia two to three weeks after therapy, this anemia being manifest only by routine blood count. Electrocardiographic changes during the treatment, which consisted of inversion of T_3 and diminished amplitude in T_2, have been seen a few times. I do not, however, attach any clinical significance to either of these two changes.

DR. SAMUEL GOLDBLATT, Cincinnati: I want to report a slight modification of the technic used in the treatment of 100 Negro patients. My associates and I administered to these patients 1,200 mg. of mapharsen by daily single injections of 100 mg. No serious reactions were noted. There were considerable nausea, vomiting and diarrhea. With the continuance of treatment, however, an apparent tolerance developed, since in many cases the amount of nausea, vomiting and diarrhea progressively decreased. In practically all of the cases a reduction of from 20 to 25 per cent in the red cell count was noted. The patients recovered from this anemia spontaneously within one month after the cessation of mapharsen treatment. There were no characteristic changes in the white count, since some patients developed a leukocytosis, some a moderate leukopenia and some remained unchanged. These patients were unselected, the first 100 persons who came in after we began the experiment. We had primaries, secondaries, early and late latent cases, some early cardiovascular cases and a number of varied types of neurosyphilis. The results in the latent and late cases, so far as the serologic reactions and spinal fluid were concerned, were disappointing. The results so far as external manifestations were concerned, such as gummas, were dramatic. A gumma of the face of some two years' duration healed within six days. The secondary manifestations healed rapidly, with the exception of the generalized adenopathy, which persisted sometimes as high as two or three weeks after all other manifestations had disappeared. In some of the cases, both the primary and secondary syphilis, in which reversals had been obtained, serologic relapses occurred within six or seven months. We did not see any cases of reinfection. We had a couple of cases of frank mucocutaneous relapse but nothing where we were worried about reinfection. This probably represents the first attempt to treat these patients in an ambulatory clinic, although I agree that the ideal proposition is to hospitalize the patient, regardless of how one treats him, during his infectious period. In an attempt to minimize even the gastrointestinal reactions, we later treated a small group of white patients with a normal 60 mg. dose daily for as high as thirty days without any type of reaction, and to date with good serologic and cerebrospinal fluid reaction. I believe, however, that before we become too enthusiastic about this method we must remember that syphilis waits twenty years to destroy our therapeutic illusions.

DR. ARTHUR G. SCHOCH, Dallas, Texas: Alexander and I have treated patients with early syphilis for the last eleven months with the syringe technic. We use the same total dosage, 1,200 mg. of mapharsen, but giving 120 mg. a day for ten consecutive days. The syringe technic is a necessity in our part of the country because our new case load in the clinic is around 300 new patients a month and about 27 per cent of them have early syphilis. We do not have hospital beds available for continuous intravenous drip. Our preliminary results are 80 per cent cures, 10 per cent failures and 10 per cent in which the results are pending. By pending I mean serologic results in which the Wassermann reaction is negative, standard Kahn test is negative and the standard Kline test is doubtful. We have in the group 70 that have completed treatment. We have seen 1 case of hemorrhagic encephalitis in which prompt recovery occurred. We have had 1 case of mild icterus following the first injection and 1 case of generalized purpura unassociated with any findings in the blood platelets or white count. In the 70 cases 44 in which a spinal fluid examination was made showed only 2 positive fluids, and they were in the 2 patients who had serologic relapse. The serologic relapse would have never been detected had we not been doing quantitative serologic studies. These two serologic relapses never showed complete serologic negativity. Improvement occurred to the point where there was 1½ units of reagin in the blood and suddenly returned with 8 to 10 units of reagin. In the entire series, there has been one clinical relapse and one very definite reinfection.

DR. LEON BROMBERG, St. Louis: I wish to ask a question. Dr. Elliott and his co-workers spoke about three fatal cases in which the autopsy findings were obscure, although there were clinical signs of hemorrhagic encephalitis. Burns and I some eleven years ago showed multiple fat embolism as the mechanism of death in such a case. The work was later confirmed by Phinizy and Brittingham. I should like to ask Dr. Elliott whether fat stains were done on the pathologic material; if not, I should be interested to get some of that material to find out whether or not fat embolism was present.

DR. IRA L. SCHAMBERG, Ann Arbor, Mich.: I should like to enter a plea against the indiscriminate use of massive arsenotherapy in late syphilis. The early control of infectiousness and the rapid and radical cure which are apparently brought about in a high percentage of patients with early syphilis by this method suggest that it may prove to be superior to conventional treatment in this stage of the disease. However, in most forms of late syphilis the problem of infectiousness is negligible, and speedy therapeusis is of little value and may even be harmful. Is it important whether a gumma of two years' duration is healed in six days by this method or in two weeks by routine treatment? Is the healthy person with late latent syphilis benefited more by an immediate massive "slug" of arsenic than by more prolonged therapy? In cardiovascular syphilis the dread Herxheimer reaction and the therapeutic paradox have taught the need for mild initial treatment. Massive arsenotherapy is strongly contraindicated in any form of cardiovascular syphilis. The increased hazard of this treatment in other types of late syphilis also needs to be considered. In healthy young adults massive arsenotherapy has a slightly higher mortality rate than does routine treatment. Might not this danger be increased in older patients with late syphilis?

DR. MARION B. SULZBERGER, New York: If one continues to give a potentially allergenic drug of the type of the arsphenamines—or other arsenicals such as mapharsen—daily without interruption over a period of ten days, one gets finished with one's treatment before the sensitization to these substances has had an opportunity to develop. Moreover, if, as Frei and I have shown, there is a certain parallelism between sensitizations to this type of arsenical allergen and sensitizations to other known allergens such as horse serum (in guinea pig anaphylaxis) it is obvious that one cannot sensitize, provided one gives daily doses. In other words, one cannot make a guinea pig sensitive to horse serum if one gives it daily injections of horse serum—in order to sensitize it one must allow an interval to elapse between the first and subsequent administrations of the allergen. And once this state of so-called antianaphylaxis has been created the animal cannot be sensitized and cannot be killed by this allergen in question. This phenomenon of antianaphylaxis might explain the reduction in the incidence of certain untoward phenomena in the continuous intravenous drip method—in which the potential allergen is given over a period of days without interruption as contrasted with the older methods in which there are periods of days or weeks which lapse between one administration and another. Of course, if the daily administration actually prevents sensitization that would be a great advantage, because a good many of the unpleasant sequelae due to arsenicals are today considered to be due to their allergenic or sensitizing effects. As Dr. Schoch has just said, it appeared to me on studying the reports that have been published to date that there was still a gap in these experiments. Dermatologists had a long time ago demonstrated that neoarsphenamine given in massive doses with a small syringe was too "toxic" to be practicable. The same drug (neoarsphenamine) given by present investigators by the new intravenous drip method also proved to be therapeutically effective, but again too "toxic." Then, with mapharsen given by the intravenous drip method, one finds that the untoward reactions are sufficiently reduced to make the method worthy of further serious consideration. The question still remains open, Might not mapharsen, given by another method—for example daily, in small syringes—also prove to be effective and not too dangerous? Is the reduction in accidents not perhaps due to the relative safety of mapharsen as compared with neoarsphenamine rather than to the newer method of administration? I think that question requires further study.

DR. HAROLD N. COLE, Cleveland: I wish to add a word of commendation for this new method that has been suggested by the New York group. But, on the other hand, I agree with Dr. Baehr that we must be very conservative. I know of several other deaths that have occurred. This is no method of therapy that is to be used indiscriminately. It is still very much in the experimental phase and it should be employed only in well equipped university and syphilis clinics.

DR. HAROLD T. HYMAN, New York: To respond to Dr. Sulzberger, we have retreated 27 patients. There have been no allergic manifestations. This presentation is our valedictory to active work with our method in the treatment of early syphilis. The critics of the work have stressed its toxicity, the necessary institutionalization of the patient and our discontinuance of active work in early 1940. The toxicity of the five day treatment is decidedly less than that of routine conservative treatment, with possible exception of the cerebral manifestations which are commonly termed "hemorrhagic encephalitis," which is a manifestation of idiosyncrasy, not overdosage. Were the truth known, I am convinced that this grave complication would be found to occur equally in all forms of routine arsenotherapy. The necessity of institutionalization we regard not as a drawback but as a virtue. It is shocking to think that the patient with infectious syphilis is permitted to mingle freely with the community. Particularly with men mobilized and living in barracks, institutionalization should be mandatory in early syphilis. For the institutionalized patient the continuous intravenous drip is the method of choice. Multiple injections must not be attempted as a compromise to avoid institutionalization. Those who employ this method will probably experience increased toxicity. I do not believe that any of the available arsenicals will replace mapharsen. Its value is best illustrated by the incidence of 35 per cent of peripheral neuritis with neoarsphenamine against 1.7 per cent with mapharsen; of 1 treatment death in 111 with neoarsphenamine against not a single treatment death in 275 patients with mapharsen. Our dosage of 1,200 mg. is avowedly established by trial and error. Lesser dosage will result in infectious relapse. Greater dosage invites significantly increased toxicity. Our discontinuance of active work has been much misunderstood. Those who interpreted our withdrawal from active work as evidence of difficulty or confession of failure are in serious error. It is our great good fortune to have our work taken up and continued by the U. S. Public Health Service. To them, as a relay runner, we pass the baton and with this symbol goes our hope that they may carry on to the now visible goal, the triumph of medicine over syphilis.

DR. DAVID C. ELLIOTT, Chicago: I cannot within the few minutes allotted to us for summary attempt to give you our impressions or answer all the questions which have been asked. The fatalities which have been reported have all occurred in our series. The total number of cases which have now been treated, i. e. since the chart was prepared and since our manuscript was approved, has been about 2,000 patients. Recalculated on this base the fatality rate has dropped slightly to 0.25 per cent rather than 0.3 per cent. The autopsies have all been done, Dr. Bromberg, in university hospitals by the professors of pathology. They have not completed the special tissue preparations of the spinal cord and brain in every instance. We have their permission to consolidate these autopsy reports and they will also be published separately with every detail that we can possibly find about the case. We agree with Dr. Schamberg of Ann Arbor, who pointed out that the method should be confined to early cases at present and not any attempt should be made to use it in late syphilis, in the sequelae, may I say, of improperly or untreated early syphilis. It is our function in the Public Health Service to attempt to correlate all these reports and to evaluate over a longer period of time than we have had the privilege of doing as yet the results and the observations of these various methods of therapy, all based on the main idea of slow intravenous drip to avoid shock and of maintaining a saturation point or plateau of arsenoxide to prevent the regeneration of subsequent families of spirochetes in the patient. I assure you that we shall continue this work of data analysis in the most dispassionate manner, for we are from the standpoint of health officers keenly interested in the potentialities which this method presents. We believe that some form of therapy similar to the one presented here today may evolve which can be relied on to give better results than we have with the ordinary schedules of treatment now available.

SERODIAGNOSTIC TESTS FOR SYPHILIS IN STATE LABORATORIES

THE 1941 EVALUATION OF THEIR PERFORMANCE

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There is an increasing appreciation of the need for a system of gaging the efficiency of performance of the laboratory tests on which the medical profession places major reliance in the diagnosis of syphilis. For the past six years the Committee on Evaluation of Serodiagnostic Tests for Syphilis has interested itself in this field and from time to time has published reports dealing with the standards of performance of tests in the state laboratories. In these publications, however, the identity of the participating laboratories was hidden by the use of code designations. It is realized that this procedure has restricted the usefulness of the material in that it has been impossible for the individual medical man to judge the efficiency of test performances in the laboratory to which his specimens were sent.

With the approval of the various state health departments, it is now desired to present the results of the most recent evaluation study without recourse to code designations of the participants.

The procedure used in the conduct of the survey may be outlined briefly. Identical whole blood specimens collected from 230 syphilitic donors and from 132 presumably nonsyphilitic donors were sent to each participant. Similar specimens were tested in the laboratories of a control group consisting of Drs. Harry Eagle of Baltimore, William A. Hinton of Boston, Reuben L. Kahn of Ann Arbor, Mich., Benjamin S. Kline of Cleveland and John A. Kolmer of Philadelphia. The Venereal Disease Research Laboratory of the Public Health Service served as a referee in the matter of the suitability of each donor for the purpose of the study. The selection of both syphilitic and nonsyphilitic donors was made from the clinics of the Department of Dermatology and Syphilology of the University of Virginia Department of Medicine under the supervision of Dr. Dudley C. Smith, from the Department of Dermatology of the University of Illinois College of Medicine under the supervision of Dr. F. E. Senear and from the Public Health Service Medical Center at Hot Springs National Park, Ark., under the supervision of Dr. Austin V. Deibert. The distribution of specimens covered a period of five weeks.

The ability of the individual test procedures to detect the presence of the reacting substance in serum from syphilitic donors is designated as "sensitivity" and is expressed on a percentage basis. The ability to exclude the presence of the reagin in serums from the presumably nonsyphilitic donors is designated as "specificity" and is also expressed by a percentage figure. Doubtful reactions are accorded a one-half credit if occurring in the serum of a syphilitic donor and a one-half demerit or penalty when recorded for the serum of a nonsyphilitic donor. A satisfactory performance is arbitrarily considered to be one which attains a sensitivity rating not more than 10 percentage points below that of the suitable control. In specificity a rating below 99 per cent is considered unsatisfactory.

This method is not considered to be a complete system for the evaluation of a serodiagnostic test, nor is it free from objection on statistical grounds. The method does, however, afford a fairly acceptable yardstick by which the standard of laboratory service may be judged in terms of the presence or absence of clinical syphilis and in terms of the results obtained in comparable examinations by the group of control serologists. A presentation of the entire material which has accumulated in the course of six annual surveys would be informative and would be attempted if space permitted. The field has been well covered, up to the current survey, in the comprehensive review prepared by Hin-

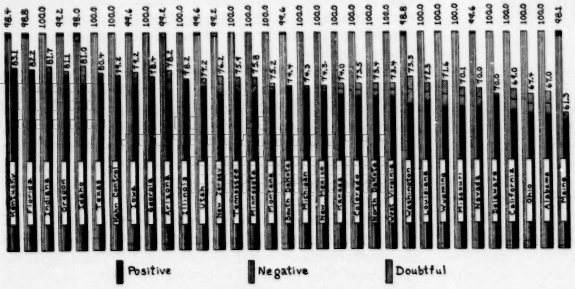

Chart 1.—Standard Kahn precipitation tests. In the charts the left column denotes specificity (results from testing serums of nonsyphilitic donors) and the right column sensitivity (results from testing serums of syphilitic donors).

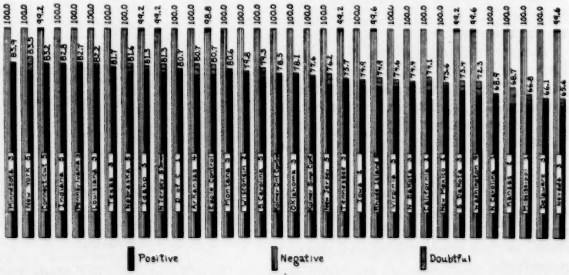

Chart 2.—Complement fixation methods: 1. Eagle complement fixation. 2. Kolmer quantitative. 3. Kolmer simplied. 4. Kolmer modified. 5. Miscellaneous complement fixation.

richsen.[1] The consecutive studies display a sustained trend toward a more efficient performance of test methods and a more uniform standard of results in the large majority of state laboratories. Contributing to this trend has been the abandonment, in many instances, of obsolete technical methods and the substitution for

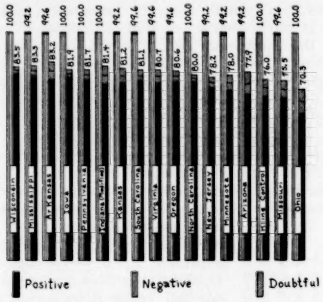

Chart 3.—Diagnostic Kline precipitation tests.

these of more efficient procedures. A contributing factor also has been the free use of the facilities which have been provided for the training of technical personnel.

The general improvement has proceeded to a point where, at this time, the statement that reliable serodiagnostic tests may be obtained in practically all parts of the country seems to be warranted.

Chart 1 portrays the results obtained in the 1941 survey by thirty-two state laboratories utilizing the Kahn standard procedure. The control performance is that of Dr. Reuben L. Kahn of Ann Arbor, Mich. A fairly uniform level of sensitivity is maintained by a large majority of the participants. Although the graph is prepared on the basis of positive, doubtful and negative reporting, an analysis of the actual numerical readings indicates a close approximation to the control findings in many instances. An analysis of partial and complete agreement with the control performance points also to a fairly uniform use of the technical precepts of the originator of the method.

A relative freedom from penalties imposed for false positive and false doubtful findings in serums from the nonsyphilitic donors is apparent. The preponderance of penalties are incurred by laboratories operating the Kahn test at a level of sensitivity above that of the control. Further, a portion of the penalties may well be attributed to chance error, which cannot fail to assert itself in an undertaking of this magnitude.

In chart 2 are arrayed the ratings attained by thirty-two state laboratories which use complement fixation procedures. The control performances are those of Drs. Harry Eagle and John A. Kolmer. Because of the wide range of technical methods practiced by this group of participants, a numeral has been used to indicate the performances which adhere to the technics sponsored by either Eagle or Kolmer. There remains a group of distinctive methods, as represented by New York, Connecticut and Nebraska, which are entirely individual and which are designated as "miscellaneous."

As with the Kahn method, the complement fixation group displays a high degree of uniformity as regards sensitivity. Penalties for false doubtful and false positive results in the nonsyphilitic donors appear to be reduced to a practical minimum. The doubtful range in the known syphilitic group is extremely narrow, indicating precision in the carrying out of the tests and in the reading and interpretation of results.

Chart 3 is an array of the results of sixteen laboratories utilizing the Kline slide technic and chart 4 is a similar presentation of the laboratories which carry out the Hinton and Eagle flocculation methods. In each case the control performance is that of the originator of the method. The general observations noted with regard to charts 1 and 2 are largely applicable to charts 3 and 4.

It is possible that the degree of uniformity between the majority of state laboratories and their respective control, as displayed in the charts, may represent the upper limit attainable with the technical methods which are now available. If this is true, the efforts of the future may well be directed toward the maintenance of the present standards and toward the adoption of such sound advances as may be developed in the basic science. It must be remembered, however, that the state laboratories are responsible for only one fourth to one half of the total volume of serodiagnostic work. The remainder is carried out in smaller laboratory units, municipal, county, hospital and commercial. Any comprehensive plan for the general improvement of serologic standards must include this type of laboratory. An arrangement through which the state laboratory serves as an evaluating, consultative and training center for the smaller units within their respective boundaries is at present being placed in operation in some states and is under contemplation in many others. When in operation on a nationwide basis, a plan of this kind should have the ultimate effect of assuring an acceptable standard of serologic results within the known limitations of the methods which are in general use at the present time.

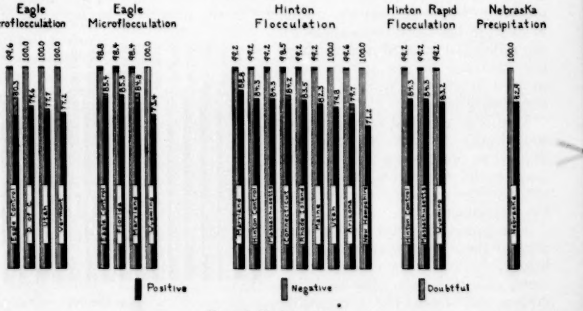

Chart 4. Various tests.

1. Hinrichsen, Josephine: Modern Serologic Tests for Syphilis and Their Interpretation by the Physician, supp. 14 to Venereal Disease Information, U. S. Public Health Service, Washington, D. C., 1941.

ANAL TUBERCULOSIS

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Anal tuberculosis does not occur very frequently unless it is complicated by rectal involvement, and primary tuberculous fistula in ano is scarcely ever seen. F. C. Smith [1] found only 6 instances of anal tuberculosis in the records of 3,700 patients with rectal disease. Petter and Fansler [2] reported that among tuberculous patients the incidence of perianal tuberculosis was 0.8 per cent and the incidence of tuberculous abscess and fistula was 5.8 per cent. In a series of 551 cases of tuberculosis these authors found 12 cases of tuberculous anal ulcer, 2 cases of tuberculosis cutis orificialis and 1 case of lupoid cutaneous tuberculosis. Berry [3] stated that fistula and abscess comprised 85.9 per cent of all perianal tuberculous lesions and listed only 2 tuberculous ulcers in 18 instances of perianal tuberculosis. The disease occurs most frequently among young adults and, according to Quénu and Hartman,[4] is more common among males.

The classification of early writers [5] is being employed with little change in present day literature.[6] The lesions may be miliary, lupoid, ulcerative or verrucous. Ulceration may occur with other types of lesions, residuums of fistulas or soft vegetations.[7] Unusual types of papillomatous lupus,[8] ulcerovegetative [9] and ulcerogummatous involvement [10] of the anus and adjacent structures have been reported.

Usually tuberculosis of the anal and perianal tissues occurs secondary to similar disease elsewhere in the body.[11] It spreads by the lymphatics and blood vessels, by direct extension and by sputum laden with bacilli. Autoinoculation may occur. Swallowed sputum has been shown by numerous investigators to be the source of the tubercle bacilli found in feces of patients with pulmonary tuberculosis. There is no apparent difference in the virulence of the bacilli in the sputum and those found in feces of patients who have tuberculosis of the lungs.[12]

The histologic structure of cutaneous tuberculosis has been studied by Montgomery in a series of nearly 200 cases in which the disease was of various types. On the basis of the clinical and histologic pictures he classified the lesions as localized and hematogenous. The histologic diagnosis of the diverse forms depends on an evaluation of the relative degrees of caseation necrosis and on the proportion of epithelioid cells, giant cells and a peripheral zone of lymphocytes and plasma cells. The position and depth of the tubercle formation plus the relationship of tubercles to blood and lymph vessels also materially assist in the diagnosis. Varying degrees of arteritis and phlebitis may indicate hematogenous dissemination. The elastic tissue is destroyed where tubercle formation occurs. Special stains for elastic tissue and correlation of histologic and clinical features may be necessary to establish the diagnosis of a hematogenous type.

We will not include a complete classification of cutaneous tuberculosis here. Tuberculosis of the anus is usually a localized cutaneous disease and may be classified as follows:

1. Inoculation tuberculosis (including the primary cutaneous tuberculous complex usually seen in infants and children). Montgomery [13] and Harrison [14] have not observed this in anal tuberculosis.
2. Tuberculosis verrucosa cutis.
3. Tuberculosis cutis luposa (lupus vulgaris).
4. Tuberculosis cutis orificialis.
5. Tuberculosis cutis colliquitiva (scrofuloderma).

Fig. 1.—Tuberculous ulcer of anal margin; like most lesions of tuberculosis orificialis, this one does not show anything of diagnostic significance.

CONSIDERATION OF CASES

The 10 patients whom we have studied were males whose average age was 36.3 years. Specimens for biopsy were obtained in 7 cases. These patients had

From the Section on Proctology, Mayo Clinic.

1. Smith, F. C.: Anorectal Tuberculosis, M. Rec. **140:** 463-465 (Nov. 7) 1934.
2. Petter, C. K., and Fansler, W. A.: Tuberculosis of the Anus and Rectum, Tr. Nat. A. Prev. Tuberc. **26:** 159-163, 1930.
3. Berry, F. B.: Perianal Tuberculosis, Ann. Surg. **99:** 593-599 (April) 1934.
4. Quénu, E., and Hartman, H., cited by Bacon.[6]
5. Allingham, William: Fistula, Hemorrhoids, Painful Ulcer, Stricture, Prolapsus and Other Diseases of the Rectum: Their Diagnosis and Treatment, ed. 4, New York, Bermingham & Co., 1882, chapter 19, pp. 232-239. Tuttle, J. P.: A Treatise on Diseases of the Anus, Rectum and Pelvic Colon, Ed. 2, New York, D. Appleton & Co., 1905.
6. Bacon, H. E.: Anus, Rectum and Sigmoid Colon; Diagnosis and Treatment, Philadelphia, J. B. Lippincott Company, 1938. Buie, L. A.: Practical Proctology, Philadelphia, W. B. Saunders Company, 1938.
7. Savignac, Roger: De quelques formes de la tuberculose ano-rectale, Arch. d. mal. de l'app. digestif **21:** 1097-1102 (Oct. 12) 1931.
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11. Brown, Lawrason, and Sampson, H. L.: Intestinal Tuberculosis: Its Importance, Diagnosis and Treatment; A Study of the Secondary Ulcerative Type, ed. 2, Philadelphia, Lea & Febiger, 1930.
12. Carvalho, A.; Vidal, C., and Rocheta, J.: Sur la virulence du bacille de Koch dans les matières fécales, Compt. rend. Soc. de biol. **127:** 246-248 (Dec. 15) 1938.
13. Montgomery, Hamilton: Histopathology of Various Types of Cutaneous Tuberculosis, Arch. Dermat. & Syph. **35:** 698-715 (April) 1937.
14. Harrison, M. W.: Inoculation Tuberculosis of the Skin with Special Reference to the So-Called Primary Cutaneous Complex of Tuberculosis, Thesis, University of Minnesota Graduate School, 1940.

no rectal tuberculosis and had no evidence of fistula in ano. Pulmonary tuberculosis existed in all 7 cases in which biopsy was performed. In 9 instances the roentgenogram of the thorax disclosed evidence of tuberculosis and in 1 case the physical findings plus the presence of acid fast bacilli in the sputum proved that tuberculosis existed. In 1 instance there was a history of resection of the cecum for hyperplastic tuberculosis. The sputum was examined in 7 cases, and acid fast bacilli were found in 4 of these cases. A specimen from only 1 patient was injected into guinea pigs and the result was positive. Serologic tests for syphilis were negative in all of the cases. No intradermal tuberculin tests were performed.

In specimens of the anal ulcers, tuberculosis was demonstrated in 6 instances and an "inflammatory reac-

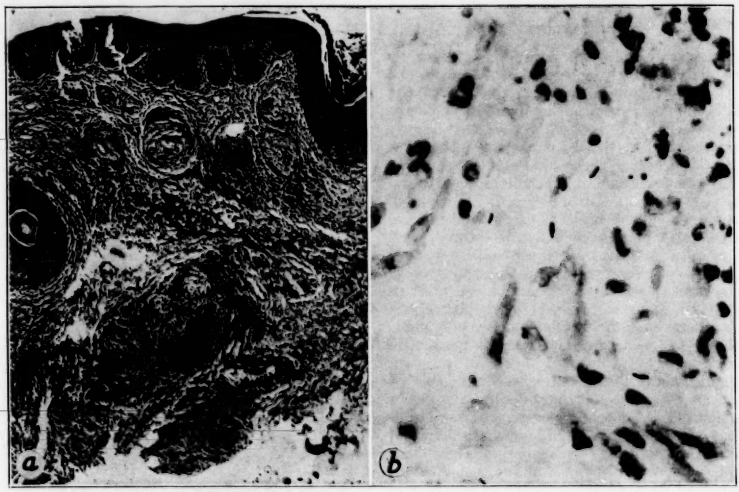

Fig. 2.—*a*, Tuberculosis cutis orificialis; discrete and conglomerate tubercles; section stained with hematoxylin and eosin (× 50); *b*, tuberculosis cutis orificialis; Mycobacterium tuberculosis in tissue; Ziehl-Neelsen stain (× 900).

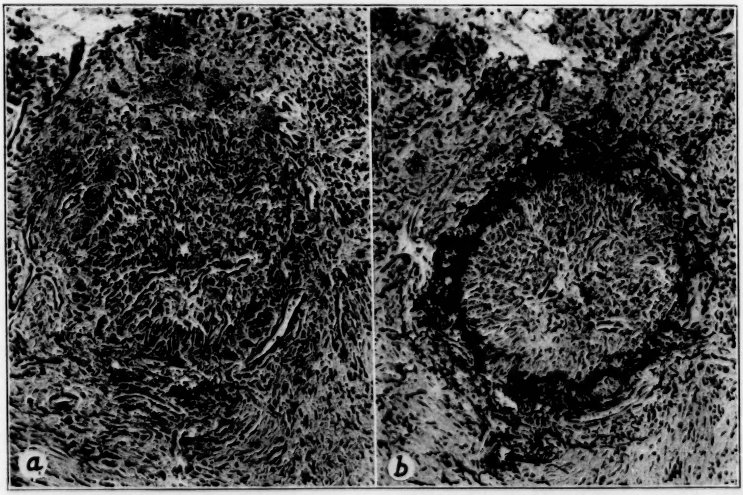

Fig. 3.—*a*, Tubercle formation in blood vessel; specimen stained with hematoxylin and eosin (× 155); *b*, tubercle formation in blood vessel; specimen stained with elastin H (× 155).

tion" was reported in 1. Often it is not possible to discover definite microscopic evidence of tuberculosis when there is a history indicative of intestinal tuberculosis, and this is true even when pulmonary tuberculosis is diagnosed and the diagnosis is confirmed by the roentgenologic examination, the physical examination and the finding of Mycobacterium tuberculosis in the sputum.

In 4 cases the lesions were classified histologically as tuberculosis cutis orificialis (figs. 1 and 2 *a* and *b*). Specific tubercle formation with varying amounts of caseation necrosis was found superficially as well as deep in the dermis. Evidence of hematogenous dissemination of the infection was observed in 1 case, in which tubercle formation occurred within a blood vessel and in which destruction of the elastic lamina could be seen (fig. 3 *a* and *b*). In another specimen numerous acid fast bacilli were noted. Some of the bacilli were adjacent to blood vessels. Early calcification of tubercles and giant cells, of the foreign body as well as of the Langhans type, were present in the specimens.

In 1 case we found the histologic structure of tuberculosis verrucosa cutis. The lesion was characterized by marked verrucous hyperplasia of the epidermis and underlying abscesses, but typical tubercle formation was absent. In the last case there was no caseation necrosis but there were tubercles composed almost entirely of epithelioid cells which were surrounded by little lymphocytic infiltration. The microscopic appearance seemed to be that of a hematogenous form of tuberculosis, such as sarcoid, rather than tuberculosis cutis luposa.

Previous anorectal surgical treatment had been employed in all of the 6 cases in which tuberculosis was diagnosed by biopsy. Multiple operations had been performed in 4 cases. Five patients dated their symptoms from their first operation, which in each case had been hemorrhoidectomy and had been performed from three months to nine years prior to their registration at the clinic. Thus the conclusion might be drawn that hemorrhoidectomy performed on patients with pulmonary tuberculosis may result in tuberculous infection at the operative site. In several instances scarring and marked contraction of the anal orifice developed.

SUMMARY

Biopsy was performed in 7 of the 10 cases of tuberculous anal ulcer. Microscopic examination confirmed the diagnosis in 6 of the 7 cases. In the seventh case the microscopic findings were not conclusive of tuberculosis. All of the patients gave a history of pulmonary tuberculosis, and 1 gave a history of intestinal disease that might have been tuberculous. The histologic picture of tuberculosis cutis orificialis was observed in 4 cases. Tuberculosis verrucosa cutis was seen in 1 case, and a type of hematogenous tuberculosis or sarcoid was observed in another. Histologic evidence of the hematogenous route of dissemination in tuberculosis of the anus was noted in 2 cases. In only 1 instance was there evidence of inoculation tuberculosis. Anal operations in cases of pulmonary tuberculosis may result in tuberculous infection of the operative wound. Healing often results in anal deformity. It is difficult to understand why sputum laden with bacilli of tuberculosis may traverse the entire length of the gastrointestinal tract without involving any tissues until the anus is reached.

CORONARY THROMBOSIS (WITH MYOCARDIAL INFARCTION) TEN YEARS LATER

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Twenty years have elapsed since coronary thrombosis attained recognition by the medical profession as a clinical entity of common occurrence. In the interim a number of studies bearing on its prognosis have been reported, including two of our own, fifteen and ten years ago, respectively.[1] In the majority of the earlier studies predictions as to the outcome of the disease necessarily were of limited value, except for the acute attack and for the first few years thereafter. An insufficient number of years had elapsed to permit a proper perspective in the cases with a more favorable prognosis. The prevailing opinion from the data at hand indicated an uncertain and unfavorable outlook in the majority of instances. However, it is interesting to recall that in 1926 (fifteen years ago) Hamman,[2] in describing the clinical features of this recently recognized disorder, suggested that, although it always was serious and often fatal, with further experience it might prove to be in a considerable number of cases less ominous than was at that time apparent. This prediction has been substantiated. Particularly encouraging have been occasional reports of special instances of an unusual longevity of seventeen to thirty-seven years, yet the implication for the majority of patients has been still far from comforting.[3]

Since one cannot approach with confidence the question of prognosis until the completed course of the disease in a large number of patients can be viewed in retrospect, it seemed to us desirable after the lapse of another decade to take stock of our original 1925 series of patients, on whom an interim report (with additional cases) was made in 1930 (published in 1931). The outcome for a considerable number has been much more favorable, we believe, than is generally appreciated and hence warrants further emphasis.

Our original series consisted of 200 consecutive patients with coronary thrombosis, or a clear history of it, seen in consultation by one of us (P. D. W.) in the decade between 1920 and 1930. The general features of this group as to age, sex and coexisting disease were described in the report published in

From the Massachusetts General Hospital.

Read before the American Clinical and Climatological Association, White Sulphur Springs, W. Va., Oct. 28, 1940.

1. These studies include:
White, P. D.: The Prognosis of Angina Pectoris and of Coronary Thrombosis, J. A. M. A. **87**: 1525 (Nov. 6) 1926.
Parkinson, J., and Bedford, D. E.: Cardiac Infarction, Lancet **1**: 188, 1928.
Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine, **8**: 245, 1929.
Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, Am. Heart J. **5**: 705, 1930.
White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis, ibid. **7**: 1, 1931.
Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies, with Especial Reference to Prognosis, J. A. M. A. **104**: 2063 (June 8) 1935.
Middleton, W. S.: The Prognosis and Treatment of Coronary Occlusion, Minnesota Med. **18**: 710, 1935.
Willius, F. A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**: 1890 (May 30) 1936.
Palmer, J. H.: The Prognosis Following Recovery from Coronary Thrombosis, Quart. J. Med. **6**: 49, 1937.

2. Hamman, L.: Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**: 273, 1926.

3. White, P. D.: Longevity After Coronary Thrombosis, J. A. M. A. **100**: 233 (Jan. 28) 1933; A New Record in Longevity After Coronary Thrombosis, ibid. **108**: 1796 (May 22) 1937. Drake, E. H.: Long Survival Following Coronary Thrombosis, Am. Heart J. **20**: 634, 1940.

1931. It was noted then that 101 patients (50 per cent) had died. At present we are principally concerned with the course of the remaining patients during the next decade. It seems best, however, to view as a whole the after-history of the first ten years for the entire group, since this represents the interval which has elapsed for all. In many of the earlier cases a considerably longer period has passed since the onset, but the full course for the entire group will still require, we hope, another decade or even longer for completion.

TABLE 1.—*"Immediate" Mortality and Course of Survivors in Two Hundred Cases of Coronary Thrombosis*

"Immediate" Mortality, 4 Weeks	Subsequent Course of 162 Survivors	
	Died Within 10 Years	Survived 10 Years
38 *	112	50
19 per cent	69 per cent	31 per cent
By Weeks	By Years	29 Still Living
1.....23	1.....30 6.....10	Longest survival, 25 Years
2..... 8	2.....17 7..... 4	
3..... 5	3.....17 8..... 4	
4..... 2	4.....10 9..... 5	
	5..... 7 10..... 8	

* Forty-four per cent of the patients seen by us were in the acute stage.

The Ten Year Status.—We have summarized in table 1 the condition of the 200 patients ten years after their initial coronary thrombosis.[4] We believe that it is important in a consideration of the prognosis of this disease to distinguish between (*a*) the outcome of the acute myocardial infarction, complicated as it is by the risks and uncertainty of heart failure, myocardial rupture, fatal arrhythmias and secondary embolism, and (*b*) the later course of coronary disease in persons who survive this critical period.

"Immediate" Mortality.—In the present study we have included under the designation "immediate" mortality patients who died during the first four weeks. This represents an arbitrary interval, but for the majority of patients it is perhaps adequate to cover the chief complications of the acute attack, and it conveniently serves our purpose in contrasting this group who died with the subsequent course of the group who survived. The latter group consisted of 162 patients and in table 1 is divided into those who died in the course of the next ten years and those who survived this interval. Special data bearing on the outcome are summarized in tables 2 and 3.

TABLE 2.—*Subsequent Course of 162 Patients*

Recovery	Cause of Death: Coronary Insufficiency	Congestive Failure	Non-cardiac Condition	Unknown	Living (10 Years)
Complete (55 cases)..... 34%	18	1	3	2	31 (56%)
Limited by angina pectoris (63 cases) 39%	34	2	4	4	19 (30%)
Limited by dyspnea..... (44 cases) 27%	6	33	5	0	0
	58 (35%)	36 (22%)	12 (8%)	6 (4%)	50 (31%)

4. We have been unable to trace the later course of 9 patients of the original 200. In order to simplify the present study, they have been replaced by the next 9 consecutive patients with coronary thrombosis who came under our observation, all of whom were seen more than ten years ago.

As shown in table 1, 38 patients died during the early, unstable period, the majority (23) during the first week, with a progressive diminution by weeks thereafter. In properly appraising this incidence of early fatalities, it must be remembered that our series is drawn from a consultation practice and that in many instances the patients had survived the critical period before they came under our observation. Actually, of the total 200 patients, 86 were seen during this early period, so that the death of 38 represents a mortality of 44 per cent of those with acute thrombosis. This is unusually high in comparison with the mortality of 16 per cent reported by Conner and Holt [1] for initial attacks and more nearly approaches the even higher figure of 50 per cent suggested by Levine.[1] We believe that our recorded mortality (as well as that of Levine) is probably too high as a general index of the outcome of the initial attack of coronary thrombosis, since our series contains essentially the classic cases, in which at that time the disease was being recognized and hence was more severe; moreover, the request for special consultation was prompted in many instances by the evident unfavorable condition of the patient. Therefore, it is probable that, considering the frequency of mild myocardial infarction now being recognized by improved electrocardiographic technic (especially since the introduction of lead 4) and other laboratory procedures (determination of the sedimentation rate of the red blood corpuscles) and judging from our experience in the last decade, an early mortality as low as 10 to 15 per cent, a figure even below that given by Conner and Holt, is nearer the truth.

TABLE 3.—*Factors in Mortality*

	"Immediate" Death (38 Cases)	Death Within 10 Years (112 Cases)	Survival for 10 Years (50 Cases)
Sex: ♂ = 84%.....	68%	84%	94%
♀ = 16%.....	32%	16%	6%
Age at onset, average = 56....	61 years	57 years	51 years
Hypertension, 31%.....	37%	32%	2.6%

Subsequent Course.—Our chief interest at present concerns the after-history of the remaining 162 patients. Of these, 112 (69 per cent) died during the decade following their acute thrombosis and 50 (31 per cent) survived this period. It will be important to record later the ultimate fate of the 50 during the second decade; suffice it to say here that at present (1940) 21 have died and 29 are alive. Of those who survived the acute attack but died later during the next decade (column 2, table 1), the first year accounted for the greatest number (30 patients); thereafter the distribution of fatalities by years appeared not very significant.

Degree of Recovery.—Approximately one third (34 per cent) of the 162 patients who survived the acute attack recovered completely, in that they were able to carry on without cardiac symptoms (table 2). It is probable that with some, at least, the level of later activity was either consciously or unconsciously modified by their previous experience. As would be expected, the course of this group was the most favorable; more than half (56 per cent) survived the first decade. Of those who died after temporary "complete" recovery, coronary insufficiency accounted for most of the deaths (18 of 24 patients, or 75 per cent). Of the 18 patients who succumbed to failure of the coronary circulation,

11 had another and fatal occlusion; 6 died suddenly, presumably of acute coronary insufficiency (and ventricular fibrillation), and 1 died during severe angina pectoris. It is of interest that only 1 in the group who completely recovered had congestive failure later.

In contrast to the group who completely recovered, a second group of 63, or slightly more than one third (39 per cent) of the 162, were limited thereafter by angina pectoris on effort. Nevertheless, 19 (30 per cent) survived the ten year period. A slightly higher proportion (34 of 44 patients, or 77 per cent) died later of coronary insufficiency. We would have expected, perhaps, a somewhat higher figure. Of these 34, 11 had a subsequent fatal occlusion, 14 died of increasingly severe angina pectoris and 9 died suddenly. Again it is of interest that only 2 later had progressive congestive failure.

Finally, among the remaining 44 patients (27 per cent) dyspnea on exertion (myocardial insufficiency) was chiefly responsible for limitation of activity, although some had both angina pectoris and dyspnea. The unfavorable significance of breathlessness, either with or without substernal oppression, as a limiting symptom is strikingly displayed in the last column of table 2; none with dyspnea survived the ten year period. Furthermore, in contrast to the preceding two groups, congestive failure rather than coronary insufficiency was chiefly responsible for death (among 33 of 44 patients, or 75 per cent).

Thirty-three of the 50 patients who survived the first decade were limited by angina pectoris as they entered the second decade, and 9 of these had one or more later attacks of coronary thrombosis; the remaining 17 were without cardiac symptoms, although 6 had further attacks of coronary thrombosis, from which they completely recovered.

OTHER CONSIDERATIONS

In our search for factors which may have some bearing on the ultimate outcome, three seemed worthy of note.

1. *Sex.*—The unusual preponderance of men with coronary disease has been commented on since Heberden reported on the first series of 100 patients with angina pectoris in 1772. Only 3 of Heberden's patients were women. In our group of 200 patients with coronary occlusion, 84 per cent were men and 16 per cent were women. Twice as many women as men died immediately (within four weeks). Furthermore, and perhaps partly for this reason, few women survived the ten year period (table 3).

2. *Age at Onset.*—It has been the experience of others as well as ourselves that patients with coronary thrombosis in the younger age groups (third and fourth decades) have a more favorable outlook than those in the later decades. The outcome in the present series is in accord with previous reports. Patients who succumbed to the acute attack averaged ten years older than those in the group with the most favorable prognosis, who survived the first decade (table 3).

3. *Hypertension.*—Thirty-one per cent of the patients were considered to have hypertension with a persistent systolic blood pressure of more than 150 mm. of mercury or a persistent diastolic pressure of more than 100 mm. There seemed to be no striking effect of slight or even moderate degrees of hypertension on the outcome of the acute attack or on the status during the first few years thereafter. However, the added burden on the heart over a period of years is suggested by the relatively few patients with hypertension who survived the ten year period (table 3).

SUMMARY AND CONCLUSIONS

1. The after-history for the first ten years of 200 patients with coronary occlusion and acute myocardial infarction seen in consultation in the decade between 1920 and 1930 has been completed and the ten year status recorded.

2. Of the entire series, 38 (19 per cent) died during the first four weeks after their initial attack. We have designated their deaths as the "immediate" mortality.

3. Of the remaining 162 patients, almost one third (31 per cent) have survived the ten year period. Another decade, or even longer, may be required to complete the after-history of this group.

4. Our analysis indicates a favorable outcome of coronary thrombosis in a larger percentage of cases than is generally appreciated.

5. Finally, since more cases of mild coronary thrombosis (myocardial infarction) are now being recognized than was possible during the decade when this series was assembled, even more favorable reports are to be expected in the future.

Clinical Notes, Suggestions and New Instruments

THE BLANKET SPLIT SKIN GRAFT FOR COVERING LARGE GRANULATING AREAS

H. O. McPHEETERS, M.D., AND HARVEY NELSON, M.D., MINNEAPOLIS

So much has been written on the subject of skin grafting over granulating areas that further papers can do little more than repeat what has been said. The last presentation of Dr. Sumner L. Koch in *Surgery, Gynecology and Obstetrics* in January and February 1941 is so complete in every detail and covers every phase of the subject so well that little can be written that is really new. We do feel that in one particular we can add to the literature and for that reason are making this report.

Small granulating areas can be easily and quickly covered by most of the accepted technics with the razor grafts of Blair and Brown and their associates or with the small deep grafts of Davis. At times the implantation seed grafts of Braun can be used to advantage. In the resurfacing of large areas involving a complete loss of the skin of an entire thigh or leg, these methods have definite shortcomings. An experienced artist in this work can use the suction cup of Blair-Brown and actually cut fairly wide and long strips of skin and, by placing them over the area one after the other, can tack them to the granulating bed and finally cover the granulations. While this method is successful in the hands of the experienced operator, we have often seen unhappy results following its use because of the technical difficulty of cutting grafts of uniform thickness. If the grafts are taken too deep the donor area must be regrafted or healing will be slow and a keloid may develop. At times the graft may be so thin that it is of no value. As a rule, only the artist can get a strip more than 2 inches (5 cm.) wide at one time. Most of these objections can be avoided by the use of the calibrated grafts as taken with the Padgett dermatome.

For the information of those not acquainted with this instrument, the dermatome consists of a drum with a surface 4 by 7

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inches (10 by 18 cm.) with a blade of razor steel set close to the surface which can be adjusted by means of calibrated screws to any thickness from the drum face. In this way the thinnest razor graft can be cut or the full thickness of the skin can be taken if it is so desired. A special glue is painted on the drum surface as well as on the skin of the donor area after the proper preparation. This is allowed to dry well. The face

Fig. 1.—Extensive gasoline burn of both lower extremities. Granulations ready for grafting.

of the drum is then applied to the skin with a firm pressure and gradually rolled backward while the blade is rapidly moved back and forth against the skin as it is lifted by the adhesive effect of the glue. This shaves off the graft at any predetermined thickness and the full width of the drum if desired. The graft is then easily removed from the drum and applied over the granulating area to be covered and sutured well in place. It is important to make many perforations in the graft to permit the escape of the serum that would otherwise accumulate under it.

A careful search of the literature makes no mention of what we have termed the "blanket graft." We believe that we are the first to make use of and report this idea. It is particularly adapted to and used in covering an extensive granulating area such as an entire thigh, a large part of the back or body elsewhere.

In applying this idea we have made a pattern of the area to be covered by tailoring a sheet of gutta-percha to fit it exactly. This is then pinned on an ordinary drawing board covered by a warm moist towel. The grafts are then placed over this pattern one after the other and sutured together to

Fig. 2.—Small blanket graft about knee and calf.

conform to the pattern. The excess skin over the edge of the pattern is trimmed off and sutured elsewhere. In this way we have made a tailored sheet of skin graft, easily sutured together over the firm base and just the right size and shape. It is a simple matter to apply this "blanket graft" over the entire granulating area at one time and adjust it to fit. In this way the graft does not need to be sutured to the granulations, which bleed so easily, but only to the edges of good skin on all sides. This also provides good tissue to suture through and which bleeds but little and will stand the tension needed to hold the graft in place. Much time can be saved by suturing the individual grafts together on the table rather than on the patient, and it can be done far better.

In one particular case we prepared one graft with a total area of 176 square inches, or 1,100 square centimeters, and a second graft of 149 square inches, or 931.25 square centimeters. We believe that the larger of these two is the largest "blanket graft" that has ever been reported in the literature. It is nearly 200 square centimeters larger in total amount of skin transferred at one sitting than we can find any report of. In spite of the extent of these grafts, the procedure was simple and easy and the end result was as good as with any small graft, the first graft taking 92 per cent and the smaller graft 90 per cent, so that no subsequent grafting was necessary.

It is of the utmost importance that all the principles of skin grafting as laid down by Koch, Padgett, Blair, Brown, Douglas and others be followed here as elsewhere. The grafts must be kept moistened with warm physiologic solution of sodium chloride all the time. Failure is often the result of this having been forgotten. The grafts must be immobilized, held firmly in place for at least five days without dressing and then firm pressure continued for the next week. At each dressing great care must be used not to lift off the graft that is just beginning to adhere. Grafts over granulating surfaces must

Fig. 3.—Large blanket graft: seven drum sheets taken from patient's back.

be kept continuously moistened with physiologic solution of sodium chloride after the operation. Pie crusting the grafts prevents the accumulation of serum. Support must be maintained to the area to prevent accumulation of edema until the graft has taken well and has become normal skin once more.

CONCLUSIONS

Large granulating areas are more easily and properly covered with large split sheets of skin rather than with many Thiersch or pinch grafts, as is so often done.

These grafts can often best be made by the use of the Padgett dermatome.

The preparation of a "blanket graft" for application over the entire surface at one time we believe to be original, since we find no mention of it in the literature on this subject.

We prepared and placed two blanket grafts in the case illustrated here. One covered a total area of 176 square inches, or 1,100 square centimeters, while the other covered 149 square inches, or 931.25 square centimeters. The large graft took 92 per cent and the other took about 90 per cent.

The technic and general principles used were those advised and recommended by Dr. Sumner L. Koch in *Surgery, Gynecology and Obstetrics* in 1941.

63 South Ninth Street.

Special Article

GLANDULAR PHYSIOLOGY AND THERAPY

PRESENT STATUS OF COMMERCIAL ENDOCRINE PREPARATIONS

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This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the author and do not necessarily represent the views of the Council.—ED.

INTRODUCTION

In the past few years physicians have had clinical experience with numerous potent endocrine preparations, many of which are pure chemical compounds. The chemical structure of most of these compounds has been identified and their physiologic activities thoroughly studied in the laboratory. With the advent of these, physicians have become well aware that preparations of desiccated ovary, testicle, thymus, pineal gland, prostate, mammary gland and other organs or simple extracts of these tissues, which have been on the market many decades are unscientific and that their physiologic activities are insignificant. Evidence supporting claims of therapeutic value for such products is either completely lacking or based on fragmentary reports or testimonials. In view of the fact that there are at present on the market pure potent endocrine principles whose effects are well known and whose properties have been investigated scientifically, there is no justification for the use of preparations whose activity is obscure and whose therapeutic effectiveness remains, after many years, unestablished. The wastefulness of prescribing these "gland" products is so apparent that the Food and Drug Administration issued a trade notice against the marketing of one type of such preparations, i. e., ovarian extracts in which neither estrogenic nor progestational activity can be satisfactorily demonstrated. A recent editorial in THE JOURNAL called the attention of physicians to this action as follows:[1a]

> . . . Except for the thyroid and perhaps posterior pituitary, products derived from a few grains of desiccated glandular material have never been proved to be effective in endocrine therapy.

The Council on Pharmacy and Chemistry has repeatedly exposed such obsolete preparations as worthless and has warned the medical profession against the insidious advertising and sales policies of those firms which promote them. Now it is gratifying to learn that the Food and Drug Administration has ruled against one type of these unscientific remedies:

> "NOTICE TO MANUFACTURERS OF PREPARATIONS OF OVARY:
>
> "There are on the market drug products in liquid form designated as 'Ovarian Extract' or by some similar title. In some instances these products have been found not to contain the known therapeutically and physiologically active constituents of ovary, namely, those having estrogenic and progestational activities. The Food and Drug Administration is of the opinion that such inert or essentially inert preparations when sold as 'Ovarian Extract,' or under any other designation or under labeling which states or implies that such active principles are present, are both adulterated and misbranded as those terms are defined in the Federal Food, Drug and Cosmetic Act."
>
> Numerous other "gland" products, relics from the ancient endocrine armamentarium, deserve similar condemnation.

ESTROGENS

There are more preparations of estrogenic substances on the market than of any other endocrine product. This popularity is probably due to the fact that estrogen therapy has proved reliable and effective under the proper conditions. The Council on Pharmacy and Chemistry has up to the present time recognized the value of estrogens in the following conditions:[1b]

> . . . the treatment of symptoms of menopause, natural or artificial, of certain other conditions related to deficiency of estrogen including senile vaginitis, kraurosis vulvae and pruritus vulvae and of gonorrheal vaginitis of children.

Although there have been numerous reports on the use of estrogens in a variety of other conditions, both endocrine and nonendocrine, it has yet to be adequately demonstrated that such therapy is of proved value in routine practice.

The estrogens marketed at present are of several varieties. Many are relatively simple extracts of urine obtained from pregnant women or mares. Others are crystalline estrogens obtained from natural sources or are natural estrogens modified by chemical procedures. Recently completely synthetic estrogens have become available, and one of these is now marketed in this country.

The choice of an estrogen for clinical use is still somewhat of a problem to the physician. The flood of advertising material constantly washing up on his desk with arguments in favor of one particular estrogen and claims for superiority based on laboratory experimentation is most confusing. Then, too, the prices of the various products differ considerably and it is frequently difficult for the physician to select what he considers an effective, reliable estrogen at an economical cost. This unfortunate situation is in part due to the lack of a satisfactory nomenclature and concise therapeutic standards.

In 1936, on the recommendation of the Advisory Committee on Nomenclature, the Council adopted the terms "estrone," with its synonym "theelin," and "estriol," with its synonym "theelol," for crystalline ketohydroxyestrin and trihydroxyestrin, respectively, and "estradiol" for dihydroxyestrin. A more difficult problem has arisen in the establishment of the nomenclature for preparations of mixed estrogens. These noncrystalline estrogens are usually derived from the urine of pregnant mares and the urine or placentas of pregnant women. Until recently there was no official term for these preparations, which contain mainly estrone and varying amounts of phenolic compounds, some of which are estrogenic. Numbers of these preparations are on the market, and each is known by a proprietary name which undoubtedly causes considerable confusion as to the nature of the preparation. The Council has recently adopted the terms "Solution of Estrogens" and "Solution of Estrogenic Substances" to signify such preparations in solution. The Council has also advised that the source of each preparation should be stated on the label. Estradiol and its compounds are known only by their proprietary names. A simplification of this nomenclature would undoubtedly be appreciated by the medical profession.

1. (*a*) Ovarian Preparations, editorial, J. A. M. A. **114**: 415 (Feb. 3) 1940. (*b*) Estrone (Theelin) in New and Nonofficial Remedies, Chicago, American Medical Association Press, 1941, p. 376.

The question of standardization of the estrogens is still a major problem in therapy. The establishment of the international standard for estrone has helped somewhat; 0.0001 mg. of estrone equals 1 international unit (1 I. U.). This international standard is not to be confused with the international standard for estradiol benzoate, 0.0001 mg. of estradiol benzoate being 1 international benzoate unit (1 I. B. U.). This standardization was attempted in order to avoid the variations inherent in bioassays in different laboratories. Some of the factors which influence the results of bioassays are (1) difference in the responses of animal colonies, (2) variation in technics, (3) species difference and (4) lack of uniformity in determining the end point of activity as observed in vaginal smears. The wide fluctuation in bioassays compared with weighed amounts of estrone is indicated in table 1, showing the number of international units of estrone equivalent to 1 biologic unit as obtained by different workers.

TABLE 1.—*A Comparison of One Biologic Unit of Each of a Number of Oil Solutions of Estrone with the International Standard (0.0001 Mg. Equals 1 International Unit)*

Authors	1 Mouse Unit	1 Rat Unit
Hain and Robson	0.9 I. U.	33 I. U.
Schoeller, Dohrn and Hohlweg	5.0 I. U.	25 I. U.
Pedersen-Bjergaard	3.5 I. U.	28 I. U.
Emmens[2b]	1.5 I. U.	.....
Doisy	0.5 I. U.	
D'Amour & Gustavson	.....	13 I. U.
Hinglais and Hinglais	.....	25 I. U.
Burn	.....	9.6 I. U.
Mazer and Israel	.....	10.0 I. U.
Gerard	.....	41 I. U.
Rowe & Simond	.....	3.0 I. U.

The standardization of noncrystalline estrogens in terms of international units may be misleading, since the international unit refers only to crystalline estrone. Emmens[2b] has pointed out significant differences in assays when impure estrogen preparations are used. He has concluded that "we cannot in practice arrive at a trustworthy estimate of the nature or amounts of the estrogens present in an impure extract." With highly purified estrogen preparations, containing traces only of contaminants, assays in terms of international units may be practical for clinical purposes if the necessary controls are included in such a study. Standardization of the experimental animals with weighed amounts of estrogens increases the reliability of bioassays.[2a]

TABLE 2.—*The Ratios of the Potencies of Oil Solutions of Estrone and Estradiol in Rats and Mice Obtained by Various Investigators*

Authors	Estrone-Estradiol Ratio in Mice	Estrone-Estradiol Ratio in Rats
Schoeller, Dohrn & Hohlweg	1:0.8	1:6
Sondern & Sealey	1:6	1:2
David, de Jongh & Laqueur	1:2	1:3
Dirscherl	1:5 to 10	.....
Whitman, Wintersteiner & Schwenk	.....	1:12
Pedersen-Bjergaard	1:0.08	1:0.5
MacCorquodale and associates	.....	1:6

A more complex problem arises with assays of estradiol compounds. It has been repeatedly shown that in the rat estradiol itself is more potent than estrone. In the mouse, however, there is some evidence which indicates that estrone is more nearly equal to estradiol in activity. The ratios of activity between estradiol and estrone in mice and in rats as determined by different investigators are given in table 2. The wide variation in the results indicate that any exact conclusion regarding the relative activity of estrone and estradiol in laboratory animals is unsafe.

Some of the manufacturers of estradiol and its compounds have of late advertised that their preparations of estradiol are many times more potent than estrone for clinical purposes. There is no information which indicates conclusively that the relatively greater potency of estradiol over estrone in the rat is obtained in man. This situation is further complicated by the fact that compounds of estradiol such as estradiol benzoate or estradiol dipropionate cannot be compared directly with estrone by animal assays, since the rates of absorption of these substances differ considerably. Substances like estrone or estradiol in oil solution are absorbed relatively rapidly and produce a short estrus in rats, while estradiol dipropionate, which is slowly absorbed, produces a prolonged estrus. In view of the differences in persistence of estrous changes between estrone and estradiol dipropionate, a comparison of these in biologic units such as "rat units" is meaningless. Similarly, a comparison of estrone and estradiol benzoate on the basis of rat units is unjustified.

TABLE 3.—*The Ratios of the Potencies of Parenterally and Orally Administered Estrone in Various Animals Obtained by Different Investigators*

Authors	Parenteral-Oral Ratio in Mouse	Guinea Pig	Rat	Monkey
Sondern and Sealey	105:1	.....	75:1	.....
Pedersen-Bjergaard	62:1	19:1	198:1	5:1
Rowe and Simon	.....	.....	15:1	.....

The Ratios of the Potencies of Parenterally and Orally Administered Estradiol in Various Animals Obtained by Different Investigators

Sondern and Sealey	500:1	.....	97:1	.....
Pedersen-Bjergaard	75:1	1.8:1	620:1	20:1
Rowe and Simon	.....	.....	15:1	.....

It would seem that compounds of estradiol such as the benzoate and the dipropionate would be more efficient therapeutically than estrone because the slower absorption of these compounds would result in a more protracted action resulting in less loss by destruction of the material administered, thus necessitating fewer injections. Surprisingly, there are few conclusive data available comparing the therapeutic efficiency of weighed amounts of these estrogens. There is some evidence which indicates that with administration of estrone and estradiol benzoate to human subjects the rates of urinary excretion of estrogens are equal.[3] Since estrogens are used in human subjects, it stands to reason that assays employing human subjects will give a greater measure of reliability over laboratory procedures employing animals. Such a study should be based on weighed amounts of the estrogens tested rather than on biologic units. Until such data are made available, the physician

2. (*a*) Palmer, A.: The Effect in Ovariectomized Mice of Past Estrogenic Stimulation on the Subsequent Responses to Estrogen, with Special Reference to Method of Bio-Assay, Univ. California Publ., Pharmacol. **1**: 375 (Feb. 7) 1941. (*b*) Emmens, C. W.: Reports on Biological Standards—V. Variables Affecting the Estimation of Androgenic and Estrogenic Activity, Medical Research Council, Special Report Series, no. 234, London, His Majesty's Stationery Office, 1939.

3. Mazer, C., and Israel, S. L.: Studies on Optimal Dosage of Estrogens: Experimental and Clinical Evaluation, J. A. M. A. **108**: 163 (Jan. 16) 1937.

is forced to rely to a great extent on his own clinical experience as to the comparative effectiveness of the various estrogens.

In the rat or the mouse estrogens are active to only a slight extent when administered by mouth. In such laboratory animals only a small portion of the administered estrone or estradiol escapes destruction; in other animals, including the human, however, there is evidence which indicates that these estrogens administered orally are relatively more effective. Table 3 indicates the relative efficiency of orally administered natural estrogens in several animal species. This table shows once more the difficulty of interpreting the therapeutic effectiveness of estrogens on the basis of laboratory data.

Estrogens are also effective by absorption following the application of ointments or tinctures to the skin or the insertion of vaginal or rectal suppositories. The efficiency of such methods of treatment is not as great as that by injection of oil solutions when a systemic effect is desired. Topical application is more efficient than parenteral administration in the treatment of such conditions as gonorrheal vaginitis, atrophic vaginitis and kraurosis. The following are the Council-accepted preparations of crystalline estrogens:

Estrone (Crystalline)

Source: Urine of stallions or pregnant mares.
Assay: By the international standard (0.0001 mg. equals 1 international unit).
License issued by: St. Louis University.

Product	Firm
Estrone-Abbott	Abbott Laboratories
Estrone-Lilly	Eli Lilly & Company
Theelin-P. D. & Co.	Parke, Davis & Company

Estriol (Crystalline)

Source: Urine of pregnant women.
Assay: By weight.
License issued by: St. Louis University.

Product	Firm
Estriol-Abbott	Abbott Laboratories
Estriol-Lilly	Eli Lilly & Company
Theelol-P. D. & Co.	Parke, Davis & Company

Crystalline alpha estradiol and its compounds estradiol benzoate, estradiol propionate and estradiol dipropionate are available. These compounds are prepared from the estrone derived from the urine of stallions or pregnant mares. They are assayed either by weight or in terms of rat units. Estradiol is usually provided in the form of tablets for oral administration and in ointments and suppositories for absorptive administration. The other estradiol preparations are dissolved in oil for injection purposes. While there is an abundance of evidence in the scientific literature to indicate that estradiol and its compounds are apparently potent and effective estrogens, the Council on Pharmacy and Chemistry has not as yet accepted any brand for inclusion in New and Nonofficial Remedies. Only one firm marketing such preparations has submitted its products to the Council, and these are still in the process of examination. Physicians are advised that many of the advertising claims frequently made for estradiol and its compounds are considered by the Council to be exaggerated and without adequate proof.

There are a number of noncrystalline estrogen preparations, which as a rule are refined extracts of urine from stallions, pregnant women and pregnant mares. They contain principally estrone together with varying amounts of other urinary phenols. There is no systematic study on the reliability of the assays presented by the firms which market these products. The Council has accepted the following preparation of noncrystalline estrogen:

Estrogenic Substances (Noncrystalline)

Source: Urine of pregnant mares.
Assay: Biologic—transposed to equivalents of international units.

Product	Firm
Amniotin	E. R. Squibb & Sons

Another type of noncrystalline estrogen preparation, containing principally estriol glycuronide, is also on the market. This is prepared from the human placenta. Its use is confined to oral administration.

Recently a number of synthetic preparations have been developed which possess sufficiently high estrogenic potency to suggest their use in estrogen therapy. Stilbene compounds have been intensely investigated in this respect, and it appears that the most promising of these synthetic compounds at the present time is 4,4′-dihydroxy-α,β-diethylstilbene.

In accordance with the writings of Dodds and associates,[4] who introduced the stilbene compounds for their estrogenic activity, the Council on Pharmacy and Chemistry has adopted the term "diethylstilbestrol" as the official designation of 4,4′-dihydroxy-α,β-diethylstilbene, reserving the term "stilbestrol" for the compound 4,4′-dihydroxystilbene, the mother substance, which is considerably less active than the diethyl compound. Unfortunately, the name stilbestrol has been used to a considerable extent to designate the active diethyl compound. In view of this situation, the term "stilbestrol" should not be confused with the official designation of the substance 4,4′-dihydroxy-α,β-diethylstilbene, which is diethylstilbestrol. In spite of the common usage of the terms at present, the official terminology was adopted in order to make allowance in the future for the development of additional compounds of the 4,4′dihydroxystilbene series which might promise to be efficient estrogens. There is already evidence that some of these compounds may be desirable estrogens. It is obvious, therefore, that there might be considerable confusion in naming such compounds if the diethyl compound were known as stilbestrol. With the mother substance, 4,4′-dihydroxystilbene, known as stilbestrol, compounds belonging to this series may be more appropriately named.

Diethylstilbestrol is formed from common laboratory reagents. It is not a steroid like the natural estrogens, but on hypodermic injection it is one to three times as potent as estrone when its activity is determined in the rat, and it possesses practically all the properties of the natural estrogens.[4] In the rodent, oral administration of diethylstilbestrol is usually considered to be one-half to one-third as effective as injections of estrone in oil solution. In the human subject diethylstilbestrol is also quite potent by oral administration, with some evidence indicating that the ratio of the potency of intramuscular to that of oral administration is from 2 to 5:1.[5] The convenience of oral administration of diethyl-

4. Dodds, E. C.; Lawson, W., and Noble, R. L.: Biological Effects of the Synthetic Oestrogenic Substance 4: 4′-Dihydroxy-α: β-Diethylstilbene, Lancet **1:** 1389 (June 18) 1938. Kellar, R. J., and Sutherland, J. K.: Clinical Experiences with New Synthetic Oestrogen-'Stilboestrol' (Diethyl-Stilboestrol): Report to Therapeutic Trials Committee of Medical Research Council, J. Obst. & Gynaec. Brit. Emp. **46:** 1 (Feb.) 1939. Stilbestrol, report of the Council on Pharmacy and Chemistry, J. A. M. A. **113:** 2312 (Dec. 23) 1939.

5. (*a*) Mazer, C.; Israel, S. L., and Ravetz, E.: The Synthetic Estrogen Stilbestrol: An Experimental and Clinical Evaluation, J. A. M. A. **116:** 675 (Feb. 22) 1941. (*b*) Shorr, E.; Robinson, F. H., and Papanicolaou, G. N.: A Clinical Study of the Synthetic Estrogen Stilbestrol, ibid. **113:** 2312 (Dec. 23) 1939.

stilbestrol gives this substance certain advantages over the estrogens which require injections at frequent intervals. The chief disadvantage of the therapeutic use of diethylstilbestrol is the development of unpleasant symptoms. There is considerable difference of opinion as to the incidence of these symptoms but on the average it is considered to be about 15 to 20 per cent.[6] The symptoms most commonly complained of are nausea and vomiting, dizziness and headaches. The possibility that these symptoms are the result of tissue damage has been investigated and as yet there has been no conclusive evidence that in the human subject therapeutic doses produce any lesions.[7] The incidence of unpleasant symptoms in postpartum patients is practically nil.[8] It has been considered by some investigators that these symptoms are the result of systemic reactions following the sudden introduction into the body of estrogens, which produce a state similar to that of early pregnancy.[9] Diethylstilbestrol has recently been released by the Food and Drug Administration for sale on physicians' prescriptions. The Council has not had the opportunity to consider diethylstilbestrol for acceptance.

Dihydrodiethylstilbestrol or, as it has been termed, hexestrol, is likewise effective on oral administration. The reports from England indicate that it is about equal in therapeutic efficiency to diethylstilbestrol but less liable to cause untoward reactions.[10] The only available data on the use of hexestrol in this country indicate that it is about one-fifth as effective as diethylstilbestrol following oral administration and that in therapeutically effective doses it may be less liable to produce unpleasant symptoms.[11] This compound is not available commercially.

Ethynil estradiol, a derivative of estradiol, is claimed to be relatively active by mouth. The comparatively high incidence of unpleasant symptoms, chiefly nausea and vomiting, has, up to the present time, prevented establishment of this compound as a desirable estrogen.

Implanting the natural or the synthetic estrogens in the form of crystals or pellets directly into the tissues of patients is an effective procedure for long-continued substitution therapy.[12] Such dosage forms are not on the market as yet. Recent investigations reveal that suspensions of crystalline estrone in aqueous mediums are more effective therapeutically than oil solutions of estrone.[13] An aqueous suspension of estrone behaves like an implant of crystals, since the crystals remain at the site of injection after absorption of the aqueous medium. Such suspensions are not yet available commercially.

6. Morrell, J. A.: Stilbestrol: Summary of Some Clinical Reports on Stilbestrol, J. Clin. Endocrinol. **1**: 418 (May) 1941.

7. (*a*) von Haam, E.; Hammel, M. A.; Rardin, T. E., and Schoene, R. H.: Clinical Studies on Stilbestrol, J. A. M. A. **115**: 2266 (Dec. 28) 1940. (*b*) Karnaky, K. J.: Endocrines in Gynecology and Obstetrics with Special Reference to Stilbestrol in Treatment of Uterine Bleeding—Original Research on Menstruation, Texas State J. Med. **38**: 379 (Sept.) 1940. (*c*) Freed, S. C.; Rosenbaum, E. E., and Soskin, S.: Alleged Hepatotoxic Action of Stilbestrol, J. A. M. A. **115**: 2264 (Dec. 28) 1940. (*d*) Shorr, Robinson and Papanicolaou.[6b]

8. Connally, H. F., Jr.; Dann, D. I.; Reese, J. M., and Douglass, L. H.: A Clinical Study of the Effects of Diethylstilbestrol on Puerperal Women, Am. J. Obst. & Gynec. **40**: 445 (Sept.) 1940.

9. Freed, S. C.: Recent Progress in Estrogen Therapy, Illinois M. J. **80**: 139 (Aug.) 1941. Karnaky.[7b]

10. Bishop, P. M. F.; Bowes, R. K.; Boycott, M.; Kellar, R.; MacGregor, T. N., and Murless, B. C.: Oestrogenic Properties of Stilboestrol Dipropionate and Hexoestrol, Lancet **1**: 629 (April 6) 1940.

11. Freed, S. C.; Greenhill, J. P., and Dahlberg, A.: Therapeutic Efficiency of Hexestrol, to be published.

12. Salmon, U. J.; Walter, R. I., and Geist, S. H.: Prolonged Therapeutic Effect of Subcutaneously Implanted Crystals of Ovarian Hormone in Women, Science **90**: 162 (Aug. 18) 1939.

13. (*a*) Freed, S. C., and Greenhill, J. P.: The Prolonged Therapeutic Effect of Suspensions of Estrone in Water, to be published. (*b*) Freed, S. C.[9]

PROGESTERONE

Preparations containing progesterone, the active principle of the corpus luteum, have been recommended for a large number of conditions, including menorrhagia, dysmenorrhea, preeclampsia, habitual and threatened abortion and menstrual disturbances of various sorts. The early reports in the literature on clinical investigations appear to be overenthusiastic and unreliable inasmuch as insignificant doses, as little as $\frac{1}{25}$ rabbit unit, were claimed to be effective. More recent reports on progesterone therapy concern the use of far larger quantities of the substance, chiefly in combating abortion, either habitual or threatened. The findings of Venning and Browne[14] that pregnandiol is an excretion product of progesterone offers the possibility of a method for assaying any deficiency of progesterone in human beings. It has been calculated that a daily dose of at least 5 to 10 mg. of progesterone is necessary to replace the progesterone normally secreted by the placenta. While there are indications that progesterone may be of value in the treatment of functional abortion, more evidence should be forthcoming along the lines laid down by Venning, Browne and associates before physicians accept any claim relating to this and other conditions.

The preparations of progesterone on the market are in two categories, synthetic progesterone and extracts of animal ovaries. The latter preparations contain in addition to progesterone small amounts of other lipids which are found in ovaries. Crystalline progesterone is prepared for commercial purposes by synthesis from certain steroids. While crystalline progesterone may be obtained from ovarian extracts, the procedure is too expensive for practical purposes. A synthetic preparation of progesterone mixed with other steroids having little physiologic activity is also available. There is no apparent disadvantage in administering such a preparation as compared with crystalline preparations. The international unit of progesterone has been used extensively in Europe and in this country. By definition, it is 1 mg. of crystalline progesterone; this is approximately 1 Corner-Allen rabbit unit. The Council has deferred consideration of either type of preparation owing to the fact that the evidence available in the literature does not indicate that progesterone or extracts containing progesterone have been adequately demonstrated to be of value for therapeutic purposes.[15]

Pregneninolone is a derivative of testosterone or of progesterone and possesses the unique ability of inducing a progestational-like condition of the endometrium in animals when administered by mouth; it differs from progesterone, however, in certain of its other physiologic activities. When administered by mouth it must be given in an amount about four to six times that of injected progesterone to induce similar progestational changes.[16] Recent reports indicate the possibility that it may be of value in the treatment of habitual abortion, dysmenorrhea and other conditions in which progesterone has received trials. The evidence at present is

14. Venning, E. H., and Browne, J. S. L.: Studies on Corpus Luteum Function: The Urinary Excretion of Sodium Pregnanediol Glucuronidate in Human Menstrual Cycle, Endocrinology **21**: 711 (Nov.) 1937. Browne, J. S. L.; Henry, J. S., and Venning, E. H.: The Significance of Endocrine Assays in Threatened and Habitual Abortion, Am. J. Obst. & Gynec. **38**: 927 (Dec.) 1939.

15. Progesterone, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **116**: 1523 (April 5) 1941.

16. Ellmens, C. W., and Parkes, A. S.: Some Biological Properties of Anhydro-Hydroxy-Progesterone (Ethinyl Testosterone), J. Endocrinol. **1**: 332 (Nov.) 1939. Hamblen, E. C.; Cuyler, W. K.; Pattee, C. J., and Axelson, G. J.: Endocrine Therapy of Functional Meno-Metrorrhagia and Ovarian Sterility: Oral Use of Anhydro-Hydroxy-Progesterone and Estrogens, J. Clin. Endocrinol. **1**: 221 (March) 1941.

inadequate and inconclusive, and further experimentation is required before the therapeutic worth of pregneninolone can be evaluated. The Council on Pharmacy and Chemistry has recently declared the substance not acceptable.[17]

ANDROGENS

After considerable experimental trials with various compounds and extracts having androgenic activity, it appears at the present time that the most useful preparation from a clinical standpoint is testosterone propionate. Preparations containing material from a few grains or grams of testicular material are definitely considered worthless. They are part of the ancient endocrine armamentarium which is rapidly being discarded. Testosterone propionate has been declared unacceptable by the Council on Pharmacy and Chemistry because androgen therapy is considered to be still in the experimental stage. The advertising claims for preparations of this compound have been largely exaggerated and unwarranted.[18] In the Council report it was indicated that the treatment of eunuchoidism and castration in men with testosterone propionate is effective if carried out with the proper dosage. This therapy is purely substitutional, and all beneficial effects recede soon after cessation of the therapy. Testosterone propionate is not recommended for the treatment of cryptorchism by Hamilton.[19] The "male climacteric," the period at which vasomotor and mental changes resembling menopausal symptoms occur, is a relatively rare condition, but it is stated to have responded favorably to androgen therapy. Androgen therapy of prostatism, while at first promising, has been discounted by recent work.[20] Histologic studies have shown that therapeutic doses of testosterone propionate have little or no effect on the prostate.[21]

Androgens have received therapeutic trials in the treatment of gynecologic conditions, and while there are indications that they may have some measure of usefulness in the treatment of dysmenorrhea, metrorrhagia, painful breasts and premenstrual tension, the therapy in these conditions should be left to specialists until more definite conclusions may be drawn as to the reliability of androgens in such treatment.

Testosterone propionate is available in oil solutions containing up to 25 mg. per cubic centimeter. Testosterone and testosterone propionate are incorporated in ointments for inunction purposes. Although androgens have a significant physiologic effect on percutaneous administration, the amounts present in most commercial ointments, namely, about 2 mg. of androgen per gram of ointment, would have little therapeutic effect unless relatively enormous amounts of ointment were applied.[22] Therefore the ointments on the market are considered ineffectual and their application impracticable for therapeutic purposes. Effective replacement therapy has been obtained with the implantation of pellets of testosterone and testosterone propionate. Such dosage forms are not available at present.

There has recently been prepared a derivative of testosterone which has significant activity when administered by mouth. This oral androgen, methyl testosterone, is being marketed at the time of publication. Investigations reveal that it is about one-fourth as active when given by mouth as when injected, and the clinical evidence available indicates that substitution therapy in castrate men or eunuchs requires about four times as much methyl testosterone for administration by mouth as testosterone propionate for injection. The practicability of such therapy is therefore open to question, since the average dosage for replacement of testicular function would have to be about 40 to 100 mg. of methyl testosterone a day.[23] Other androgenic preparations have little therapeutic efficacy. Such preparations are extracts of urine containing androsterone or similar steroids whose activity in the mammal is significantly less than that of testosterone.

PITUITARY PREPARATIONS

Extracts of the posterior lobe of the pituitary gland containing the oxytocic and pressor factors are well known to clinicians. Several recent reports indicate that a combination of pitressin with tannic acid results in a preparation which is absorbed slowly from the tissues, thereby giving a prolonged physiologic effect. This product, pitressin tannate, has been recommended in the treatment of diabetes insipidus. It has not been accepted by the Council. A number of preparations containing both factors have been accepted by the Council on Pharmacy and Chemistry, as well as preparations containing the individual factors:

Solution of Posterior Pituitary

Source: Animal Pituitary glands.
Assay: U. S. P. units.

Product	Firm
Ampoules of Pitocin	Parke, Davis & Company
Ampoules of Pitressin	
Pituitary Extract-Lilly	Eli Lilly & Company
Pituitary Extract-Merrell	The Wm. S. Merrell Company
Pituitary Liquid-Armour	The Armour Laboratories
Pituitary Solution-U. S. P.	U. S. Standard Products Co.
Pituitrin	Parke, Davis & Company
Posterior Pituitary Solution-Abbott	Abbott Laboratories
Posterior Pituitary Solution-Squibb	E. R. Squibb & Sons
Solution Pituitary Extract U. S. P. (Upjohn)	The Upjohn Company
Solution Posterior Pituitary (U. S. P.)-Wilson	Wilson Laboratories

There are a large number of preparations of the anterior lobe of the pituitary gland on the market. The Council on Pharmacy and Chemistry has accepted no preparation of the anterior lobe because there is no suitable evidence that such preparations are of value in therapy. Although the commercial preparations are unsatisfactory, experimental preparations have been developed in which the active principles have been isolated in a relatively pure form. It has been claimed that the lactogenic factor, for example, has been crystallized. Confirmation of this has not been made, although almost chemically pure preparations of the lactogenic factor have been developed by several groups of workers. In addition, preparations of the growth principle have been made which exert definite growth-promoting effects in hypophysectomized rats though administered in doses of fractions of a microgram.

17. Pregneninolone, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **116:** 1054 (March 15) 1941.
18. Testosterone Propionate, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **112:** 1949 (May 13) 1939.
19. Hamilton, J. B., and Hubert, G.: Effect of Synthetic Male Hormone Substance on Descent of Testicles in Human Cryptorchidism, Proc. Soc. Exper. Biol. & Med. **39:** 4 (Oct.) 1938.
20. Heckel, N. J.: Influence of Testosterone-Propionate upon Benign Prostatic Hypertrophy and Spermatogenesis: Clinical and Pathological Study in the Human, J. Urol. **43:** 286 (Feb.) 1940.
21. Sharpey-Schafer, E. P.; Schrire, I., and Shackman, R.: Testosterone Propionate: Its Effect on Histology of Prostatic Enlargement in Man, Lancet **1:** 1254 (June 3) 1939.
22. Foss, G. L.: Percutaneous Absorption of Male Hormone: Its Practical Application to Human Therapy, Lancet **2:** 1284 (Dec. 3) 1938.
23. Foss, G. L.: Oral Application of Methyl Testosterone and Its Simplification of Androgen Therapy, Brit. M. J. **2:** 11 (July 1) 1939.

Preparations of the gonadotropic factors have also been produced which have high potency and contain only traces of contaminating substances. Other factors which have been isolated in relatively pure form are the thyrotropic and the adrenotropic. None of the other active substances of the anterior lobe have been prepared to similar degrees of purity. The commercially available preparations are relatively crude in comparison with those developed experimentally. They usually contain significant amounts of several other factors and inert proteins. Furthermore, it has been demonstrated that the active substances of many of these preparations deteriorate on standing in solution. Thus, D'Amour and his co-workers [24] have demonstrated that anterior lobe preparations purchased in drug stores have little demonstrable activity. This is probably due to a characteristic of anterior lobe preparations in aqueous solution, namely, loss of potency on standing. It is quite possible that in the future more satisfactory preparations will be available for clinical use.

The League of Nations has recently set up an international standard for the lactogenic factor by providing an international powder as the basis for bioassays. Other factors of the anterior lobe of the hypophysis have not been so standardized.

CHORIONIC GONADOTROPIN

"Chorionic gonadotropin" is the official term for the gonadotropic substance present in the urine of pregnant women. Its properties differ from those of the gonadotropic substances of the anterior lobe of the pituitary gland in a number of respects as described in the chapter on gonadotropic hormones of the anterior lobe and chorionic tissue. Almost chemically pure preparations have been obtained experimentally. It is indicated that this substance is a glycoprotein.[25] The Council has recently accepted chorionic gonadotropin (follutein) for inclusion in "New and Nonofficial Remedies" but recognizes that the only condition in which the therapeutic response is of value is cryptorchism unassociated with any anatomic abnormalities that would prevent testicular descent.[26] The Council considered its use in the treatment of functional uterine bleeding in women and also in that of hypogonadism in men to be still in the experimental stage and that its use in the treatment of other conditions is unsatisfactory at the present time. Chorionic gonadotropin is standardized according to the international standard as adopted by the League of Nations. Therefore, these products may be found assayed in international units. Biologic units may differ significantly, since there is considerable variation in the types of assays performed by the different firms. Preparations in aqueous solution are subject to loss of potency on standing for several months at room temperature. The following preparation has been accepted by the Council on Pharmacy and Chemistry:

Chorionic Gonadotropin

Source: Urine or placenta of pregnant women.

Assay: International units (0.1 mg. of the international standard equals 1 international unit).

Product	Firm
Follutein*	E. R. Squibb & Sons

* The active substance is carried in glycerin. This preparation is diluted with saline solution for injection.

24. D'Amour, F. E.: The Potency of Certain Commercial Hormone Preparations, Endocrinology **26:** 88 (Jan.) 1940.
25. Gurin, S.; Bachman, C., and Wilson, D. W.: Gonadotropic Hormone of Urine of Pregnancy: Chemical Studies of Preparations Having High Biological Activity, J. Biol. Chem. **133:** 467 (April) 1940.
26. Chorionic Gonadotropin, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **113:** 756 (Aug. 26) 1939.

EQUINE GONADOTROPIN

The serum of pregnant mares during a certain stage of gestation contains large amounts of a gonadotropic substance. This substance is a chorionic gonadotropin but differs in its physiologic effect from the substance found in human pregnancy urine. It resembles more closely the gonadotropic complex of the anterior lobe of the pituitary gland. The Council recently published a report on the status of therapy with equine gonadotropin.[27] The Council stated that although this gonadotropin may be available in a relatively potent form, its use in the treatment of various gonadal dysfunctions is still unestablished. Claims have been made that it is capable of inducing ovulation in women. There is little evidence, however, that ovulation can be induced in those who do not ovulate ordinarily. Therefore, its use in the treatment of sterility in women is open to considerable question. There is also a lack of evidence that it is of any value in the therapy of testicular disorders, such as cryptorchism and abnormal spermatogenesis. Preparations of equine gonadotropin are assayed according to an international standard provided by the League of Nations. Formerly the various firms used biologic units which were considerably different, so that a rapid comparison of potencies of the preparations was difficult.

THYROID

Desiccated thyroid U. S. P. is still the most widely used preparation of thyroid gland. Some claims have been made that certain types of extracts of the thyroid gland contain the metabolic factor apart from a component which gives rise to nervous and vascular responses. There is no conclusive evidence that animal thyroid gland contains an active compound that evokes responses qualitatively different from those to thyroxin. Inasmuch as thyroxin produces effects identical with those of desiccated thyroid, there does not seem to be an adequate basis for postulating at the present time the presence of a thyroid hormone which has a metabolic effect separate from a factor which gives rise to nervous and vascular hyperactivity. The Council has accepted thyroxin, the active principle of the thyroid gland. Thyroxin may be injected intravenously. Its use is usually limited to the occasional case where it might not be practical to administer thyroid substance by mouth.

Thyroxin

Source: Animal thyroid gland.

Assay: U. S. P. units.

Product	Firm
Synthetic Thyroxin–Roche	F. Hoffman-La Roche & Company
Thyroxin Fraction	E. R. Squibb & Sons
Thyroxin (Squibb)	

PARATHYROID EXTRACTS AND OTHER CALCIUM-REGULATING COMPOUNDS

Commercial extracts containing the parathyroid hormone have been accepted by the Council on Pharmacy and Chemistry. These preparations are standardized according to parathyroid units as determined by the United States Pharmacopeia for solution of parathyroid. Their use is restricted to the treatment of parathyroid tetany. The administration of solution of parathyroid is not recommended for chronic hypoparathyroidism, owing to the fact that a resistance is effected

27. The Present Status of the Gonadotropic Hormone from the Serum of Pregnant Mares, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **115:** 1998 (Dec. 7) 1940.

after a number of injections. The following preparations of solution of parathyroid have been accepted by the Council on Pharmacy and Chemistry:

Solution of Parathyroid

Source: Animal parathyroid gland.
Assay: U. S. P. units.

Product	Firm
Parathyroid Extract–Lilly	Eli Lilly & Company
Parathyroid Hormone–Squibb	E. R. Squibb & Sons
Paroidin	Parke, Davis & Company

Certain steroids have a strong influence on the calcium content of the blood and on the elimination of calcium from the body.

For continuous treatment over long periods, activated sterols are being used with success. "Viosterol" is the official N. N. R. term for activated or irradiated ergosterol. It contains calciferol, lumisterol and tachysterol. Dihydrotachysterol is obtained from tachysterol; it has been found of considerable value in the maintenance of the normal blood level of calcium in patients with hypoparathyroidism. No preparation of this substance has been submitted to the Council on Pharmacy and Chemistry up to the time of publication. The following preparations of activated sterols have been accepted by the Council:

Activated Sterols

Source: Ergosterol.

Product	Firm
I. V. C. Viosterol (A. R. P. I. Process) in Oil	International Vitamin Corp., Inc.
Mead's Viosterol in Oil	Mead Johnson & Company
Parke, Davis & Co.'s Viosterol in Oil	Parke, Davis & Company
Stearns Viosterol (A. R. P. I. Process) in Oil	Frederick Stearns & Co.
Viosterol (A. R. P. I. Process) in Oil–Hospital Liquids, Inc.	Hospital Liquids, Inc.
Viosterol in Oil–Abbott	Abbott Laboratories
Viosterol in Oil–Merrell	The Wm. S. Merrell Company
Viosterol in Oil–Squibb	E. R. Squibb & Sons
Winthrop Viosterol in Oil	Winthrop Chemical Co., Inc.

ADRENAL CORTEX

The adrenal cortex secretes numerous steroids. Many of these steroids have no known physiologic activity; others possess properties which differ qualitatively and quantitatively. These compounds have roles in the regulation of salt and water metabolism, carbohydrate, fat and protein metabolism and other activities essential for the maintenance of health. In addition to steroids with these activities, the adrenal cortex contains small amounts of estrogens, androgens, progesterone and related compounds.

Desoxycorticosterone or its acetate is the only pure steroid available for therapeutic purposes. This compound has a powerful effect on salt and water metabolism, especially in adrenal insufficiency, but lacks other properties pertaining to the function of the adrenal cortex. It has been used to a considerable extent in the treatment of Addison's disease and in that of various types of peripheral circulatory failure. This substance is usually administered in oil solution by intramuscular injection. It has also been used dissolved in propylene glycol, to be placed under the tongue for absorption. This method of administration is about one-third to one-half as effective as injections of similar amounts in oil solution. The most efficient method of administering desoxycorticosterone acetate is the implantation of pellets where the slow continuous absorption results in economical and effective therapeutic action. This method, however, is best suited for use by specialists and may be dangerous in the hands of those who are not aware of the possibility of overdosage. When there is excessive dosage this substance is harmful; in patients with Addison's disease hypertension, edema and heart failure may develop. Fatalities have been reported from overtreatment of patients with Addison's disease with desoxycorticosterone acetate.[28] In experimental animals overdosage produces overexcretion of potassium, resulting in asthenia. In the treatment of patients with Addison's disease with desoxycorticosterone acetate, it is advisable to maintain a moderate potassium intake and a relatively low sodium intake because of the possibility of undesirable shifts in electrolyte balance. As to the treatment of conditions other than adrenal insufficiency, there is not available sufficient evidence to justify the use of this substance in other than experimental trials. It has been claimed that circulatory failure due to infectious diseases, such as pneumonia, and that observed in such conditions as surgical shock and anesthesia may be combated by desoxycorticosterone acetate. There is a lack of sufficient objective clinical data to substantiate these claims. In the treatment of an addisonian crisis, it is stated, desoxycorticosterone acetate may not be successful despite the use of large doses. Apparently other factors of the adrenal cortex may be essential in treating such states successfully. Pellets or crystals for implantation and propylene glycol solutions are not available commercially at the present time.

Adrenal cortex extract has been accepted by the Council on Pharmacy and Chemistry for the treatment of Addison's disease and for prophylactic use in preparation for operations about the adrenal glands. Adrenal cortex extract is used in conjunction with a high sodium and a low potassium intake. There have been no reports of overdosage with it. Although there is definite activity when adrenal cortex extract is administered orally, the effectiveness of oral administration is still subject to some debate. Oral therapy should not be depended on in an addisonian crisis. The treatment of conditions other than adrenal insufficiency with adrenal cortex extract is being studied in the laboratory and clinic. Conditions on the borderline of adrenal insufficiency are not considered an indication for such therapy, nor has its use in a variety of other conditions, including asthenia, infectious diseases, allergic conditions, toxemia and pregnancy, been recognized by the Council. Adrenal cortex extract accepted by the Council on Pharmacy and Chemistry is standardized according to dog units, although biologic assays of preparations of adrenal cortex extract are not entirely satisfactory. The following preparation has been accepted by the Council on Pharmacy and Chemistry:

Adrenal Cortex Extract

Source: Adrenal glands of animals.
Assay: Biologic units (1 cc. of extract is derived from approximately 50 Gm. of fresh gland).

Product	Firm
Adrenal Cortex Extract	The Upjohn Company

MISCELLANEOUS GLANDULAR PREPARATIONS

Commercial preparations of thymus gland, pineal gland and pancreas, excluding insulin, either alone or in various combinations, are available. There is no

28. Desoxycorticosterone, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **114**: 2549 (June 29) 1940.

reliable evidence that any of these preparations possesses endocrine activity. Lipocaic, according to Dragstedt and associates, is an internal secretion of the animal pancreas which prevents deposition of fat in the liver following pancreatectomy. There is considerable controversy regarding the nature of this substance and whether or not it is an endocrine secretion. The clinical value of the substance has not as yet been demonstrated. The endocrine factors from the gastrointestinal tract as described in the chapter on gastrointestinal hormones are not available commercially. Insulin and epinephrine are described in New and Nonofficial Remedies.

Council on Pharmacy and Chemistry

REPORTS OF THE COUNCIL

FOR A NUMBER OF YEARS THE COUNCIL HAS BEEN INTERESTED IN THE QUESTION OF DANGER FROM THE USE OF CINCHOPHEN AND NEOCINCHOPHEN AND PRODUCTS CONTAINING THESE DRUGS. THE COUNCIL HAS FROM TIME TO TIME MADE REVISIONS OF THE NEW AND NONOFFICIAL REMEDIES CHAPTER ON CINCHOPHEN AND CINCOPHEN DERIVATIVES TO CALL ATTENTION TO THE DANGERS INVOLVED IN THE USE OF THE DRUG, AT THE SAME TIME SETTING FORTH ITS FIELD OF USEFULNESS WHEN CORRECTLY AND JUDICIOUSLY EMPLOYED. RECENTLY THE COUNCIL'S REFEREE FOR CINCHOPHEN PREPARED A STUDY OF THE MORTALITY FROM ACUTE YELLOW ATROPHY FOLLOWING THE USE OF CINCHOPHEN. THE FOLLOWING ABSTRACT OF THE REFEREE'S REPORT HAS BEEN ADOPTED FOR PUBLICATION.

THEODORE G. KLUMPP, M.D., Secretary.

PRESENT STATUS OF CINCHOPHEN AND NEOCINCHOPHEN

The introduction of a phenyl group in the 2-position of quinoline-4-carboxylic acid yields 2-phenylquinoline-4-carboxylic acid, a compound commonly known as cinchophen. Another member of the same group of compounds is 6-methyl-2-phenylquinoline-4-carboxylic acid ethyl ester, or neocinchophen. Cinchophen and neocinchophen have been found to be useful in the treatment of acute gout, and McLester [1] reported relief of the pain of sciatica.

Because of reports of severe reactions and even death following the use of cinchophen, many physicians have considered it to be an essentially dangerous drug. Many have also held the same attitude about neocinchophen, although the latter is considered to be usually less toxic.

In 1923 Barbour and Lozinsky [2] claimed that neocinchophen was nontoxic for dogs in doses up to 50 Gm. per kilogram of body weight, as compared with the minimal fatal dose of cinchophen, which was 1.25 Gm. per kilogram. In 1930 Furth and Kuh [3] found the minimal fatal dose for rabbits to be 1.4 Gm. and 1 Gm. for cinchophen and neocinchophen, respectively. Apparently, then, there is considerable species variation. No one denies that symptoms of varying degrees and even death have been induced experimentally in animals by large repeated doses of cinchophen and that the effects on the liver in such cases closely resemble those found during postmortem examination of persons who have died of acute yellow atrophy after taking cinchophen or one of its many compounds or mixtures. However, the results of experiments with cinchophen on animals have not always been uniform: Barbour and Gilman [4] failed to cause liver damage in cats in one series of experiments by the administration of repeated doses of cinchophen or neocinchophen. The toxicity of a single oral dose of cinchophen is so slight that it may be disregarded in this report.

The first fatality showing yellow atrophy of the liver was reported by Cabot in 1925. Von Oettingen [5] tabulated 49 fatal accidents extending from 1925 to 1932 and 58 severe intoxications after the administration of cinchophen and related drugs. All the deaths reported by von Oettingen were of patients who developed jaundice after administration of the drug and died within a comparatively short time after the first sign of liver damage appeared. In 1936 it was reported [6] that there were records of 191 cases of jaundice with 88 deaths attributed to cinchophen (and neocinchophen). White [7] has estimated that approximately 100,000 pounds of cinchophen and its derivatives are used annually in the United States. Accepting that estimate and assuming that the average dose is 8 grains (0.5 Gm.), a total of 875,000,000 doses (1,000,000 pounds) were taken in the United States in ten years. However, since the 88 deaths did not occur in the United States alone but in England, Germany and what was then Austria-Hungary, there would be only one death for much more than 10,000,000 doses of cinchophen.

Snyder and his co-workers [8] attributed 18 deaths to the cinchophen group in twenty years (1913-1933). There is some apparent confusion in their figures, but they seem to indicate one death after 100,000,000 doses.

Of greater significance in the opposite direction is the statement of Weir and Comfort [9] that during ten years after 1923 19 cases of toxic cirrhosis had been seen at the Mayo Clinic and that the number of such cases continued to increase. They reported that 98 cases had been observed by others, making a total of 117 cases with 61 deaths. These include reports in the European literature and are included in the 191 cases with 88 deaths reported by Palmer and Woodall.[6] The testimony of Weir and Comfort [9] and of H. L. Bockus (communication to the Council in 1935) suggests that cinchophen may cause considerably more than one death in 10,000,000 doses. In 1933 von Oettingen [5] pointed out that the rate of accidents was about 1:500,000. It must be remembered that by no means all such accidents or even deaths are reported as such, so that these ratios are bound to be understatements in this respect; but the incidence is not large enough to be recognizable in the statistical death rate of yellow atrophy of the liver, which has remained uniform for thirty-five years before and after the introduction of cinchophen and related drugs which have been introduced since 1902.

CONTRAINDICATIONS

There has been no comprehensive study of the contraindications to the use of cinchophen. There is some diversity of opinion concerning the nature of its toxic effects, but it seems probable that the drug exerts two distinct types of toxic action: (*a*) a direct destructive action on the cells of the liver under conditions which have not yet been determined and which are relatively rare in proportion to those cases in which it is harmless; (*b*) an allergic reaction manifested especially in cutaneous rashes. The behavior of cinchophen suggests that the cutaneous reactions are allergic in character but that those in the liver are not.[10] Von Oettingen is of the opinion that cinchophen is neither accumulative nor habit forming but may cause epigastric pain, circulatory depression and kidney injury. Hench [11]

1. McLester, J. S.: Studies on Uric Acid of Blood and Urine, with Special Reference to the Influence of Atophan, Arch. Int. Med. **12**: 739 (Dec.) 1913.

2. Barbour, H. G., and Lozinsky, E.: Nontoxicity and Antipyretic Efficiency of Tolysin, J. Lab. & Clin. Med. **8**: 217 (Jan.) 1923.

3. Furth, O., and Kuh, E.: Biochemical Studies on Absorption of Ethylester of Paramethylphenylcinchoninic Acid (Tolysin) and Its Fate in Metabolism: Fate of Tolysin in Metabolism and Its Toxicity, J. Pharmacol. & Exper. Therap. **38**: 71 (Jan.) 1930.

4. Barbour, H. G., and Gilman, Alfred: Cinchophen and Paramethylphenyl Cinchoninic Acid Ethyl Ester (Tolysin): A Comparison of the Effects of Administration in Rats, J. Pharmacol. & Exper. Therap. **55**: 400 (Dec.) 1935.

5. von Oettingen, W. F.: The Therapeutic Agents of the Quinoline Group, New York, Chemical Catalog Company, Inc., 1933.

6. Palmer, W. L., and Woodall, P. S.: Cinchophen—Is There a Safe Method of Administration? J. A. M. A. **107**: 760 (Sept. 5) 1936.

7. White, E. P. C.: Study on Series of Arthritic Patients Under Continuous Mono-Iodo-Cinchophen Treatment with Special Reference to Action of Cinchophen Molecule on Liver Tract, J. Lab. & Clin. Med. **17**: 17 (Oct.) 1931.

8. Snyder, R. G., and others: The Use of Cinchophen in the Treatment of Chronic Arthritis, J. Lab. & Clin. Med. **21**: 541 (Feb.) 1936.

9. Weir, J. F., and Comfort, M. W.: Toxic Cirrhosis Caused by Cinchophen, Arch. Int. Med. **52**: 685 (Nov.) 1933.

10. Quick, A. J.: Probable Allergic Nature of Cinchophen Poisoning with Special Reference to Arthus Phenomenon and with Precautions to Be Followed in Cinchophen Administration, Am. J. M. Sc. **187**: 115 (Jan.) 1934. Fink, A. I.: Cinchophen Poisoning in Allergic Individuals: Report of Two Cases, J. Allergy **1**: 280 (March) 1930. Short, C. L., and Bauer, Walter: Cinchophen Hypersensitiveness: Report of Four Cases and Review, Ann. Int. Med. **6**: 1449 (May) 1933.

11. Hench, P. S., in discussion on Palmer, W. L., and Woodall, P. S.: Cinchophen—Is There a Safe Method of Administration? abstr. J. A. M. A. **106**: 327 (Jan. 25) 1936.

stated that cinchophen poisoning occurred most frequently among those patients who suffered from infectious arthritis. Köhne[12] stated that circulatory disturbances leading to metabolic disorders increase the danger of cinchophen poisoning.

One cannot state with absolute certainty that the onset of jaundice is always a contraindication to the further use of cinchophen, and Brugsch and Horsters[13] went so far as to employ cinchophen in the treatment of jaundice. But the consensus today is certainly that the administration of cinchophen should be stopped immediately on the appearance of any of the symptoms of poisoning. These symptoms include loss of appetite, nausea, vomiting, malaise, itching, purpuric spots, cutaneous eruptions and jaundice. It is generally agreed that cinchophen should not be used when a harmless, but equally effective, substitute is available. This can be determined only by a physician who is familiar with the physical condition of his patient and who is also in a position to detect the earliest signs of intoxication. Therefore cinchophen and neocinchophen are emphatically not drugs suitable for self medication.

Opie[14] stated that a diet rich in fats increased the susceptibility to liver damage by chloroform, probably because the fat of the liver cells fixes chloroform. Because of the similarity of the effects of cinchophen and chloroform on the liver, a diet rich in carbohydrates and poor in fats is commonly recommended for those who use cinchophen.[15]

Because compounds of cinchophen and iodine are more toxic than cinchophen alone, Davis[16] warned against the simultaneous use of cinchophen and iodides; however, Eaton[17] used iodides concomitantly with cinchophen and avoided a diet rich in carbohydrates. Quick[10] recommended that those who have a history of asthma or hay fever and those who are hypersensitive to foreign proteins should avoid the use of cinchophen. He also warns that no foreign protein, such as milk or vaccine, should be injected while cinchophen is being administered.

The treatment of acute yellow atrophy is unsatisfactory; but Opie[14] recommended a diet rich in carbohydrates and poor in fats, and Quick[10] recommended the adoption of measures for counteracting shock and toxemia due to the absorption of necrotic tissue.

SUMMARY AND CONCLUSIONS

1. Cinchophen is capable of inducing various symptoms of poisoning and a condition closely resembling acute yellow atrophy of the liver when repeated doses are administered to dogs and other animals.

2. Serious and fatal yellow atrophy of the liver sometimes follows the clinical use of cinchophen under conditions which indicate a causal relation. This appears to involve special susceptibility, which may preexist, or which may develop during the continued or interrupted use of the drug, sometimes suddenly and without warning. Although this condition is not common, it must be seriously considered because of the serious nature of the consequences when it does exist; and the drug should not be employed unless the attending physician feels that the patient's need for it fully justifies the risk, possibly for the relief of pain in certain cases of so-called rheumatism, including gout, and some types of arthritis when safer substitutes fail to afford relief.

3. There is no satisfactory evidence on which to base an estimate of the relative dangers in the use of cinchophen and neocinchophen in equally effective doses.

4. The contraindications to the use of cinchophen seem to include a condition of susceptibility to asthma or hay fever, allergic reaction to foreign proteins, liver disease, circulatory disturbances with resulting metabolic disorders, diets rich in fats and poor in carbohydrates and the onset of any of the symptoms of cinchophen poisoning.

5. Avoidance of these contraindications, special attention to the diet, and effective supervision of the patient are important, but it should not be felt that they render the drug safe.

6. There is urgent need of controlled clinical studies of those conditions in which cinchophen is used, of its relative dangers when contraindications are observed and of the treatment of poisoning induced by cinchophen or allied drugs.

12. Köhne, Gisbert: Leberschädigung nach Atophanpräparaten, Klin. Wchnschr. **17:** 887 (June 18) 1938.

13. Brugsch, T., and Horsters, Hans: Cholerese und Choleretica, ein Beitrag zur Physiologie der Galle, Ztschr. f. d. ges. Med. **38:** 367 (Aug. 13) 1923.

14. Opie, Eugene L., and Alford, Leland B.: The Influence of Diet on Healthy Necrosis and Toxicity of Chloroform, J. A. M. A. **62:** 895 (March 21) 1914.

15. Boros, Edwin: Hay Fever and Asthma During and After Jaundice: Ascites Due to Cinchophen Poisoning, J. A. M. A. **109:** 113 (July 10) 1937. Evans, G., and Spence, A. W.: Phenylcinchoninic Acid (Cinchophen) in Treatment of Gout, Lancet **1:** 704 (April 6) 1929. Eimer, Karl: Atophanvergiftung und ihre Behandlung, Deutsche med. Wchnschr. **51:** 1663 (Sept. 25) 1931. Quick.[10] Short and Bauer.[30]

16. Davis, J. S., Jr.: Relation of Neocinchophen to Question of Cinchophen Toxicity, Am. J. M. Sc. **184:** 555 (Oct.) 1932.

17. Eaton, Ernest Risley: A Systemic Treatment for Chronic Arthritis, Clin. Med. & Surg. **42:** 224 (May) 1935.

COMMUNICATION ON CINCHOPHEN AND CINCHOPHEN DERIVATIVES MADE AVAILABLE BY DR. THEODORE KLUMPP OF THE FOOD AND DRUG ADMINISTRATION

Dr. Theodore Klumpp has made available to the Council on Pharmacy and Chemistry a tabulation of the replies to a questionnaire on cinchophen and cinchophen derivatives sent by the Food and Drug Administration to the full professors of medicine, pharmacology and pathology and the clinical professors of medicine of the class A medical schools, as well as to those who had contributed to the literature on drugs. The Council believed it would make an informative supplement to its report on the present status of cinchophen and neocinchophen appearing in this issue of THE JOURNAL. The tabulation of replies as made available by Dr. Klumpp is as follows:

TABULATION OF REPLIES TO LETTERS ON CINCHOPHEN

Q.—Do you consider cinchophen and cinchophen derivatives indispensable therapeutic agents in the physician's armamentarium?

No	217	No	82%
Yes	36	Yes	14%
Disqualified	13	Disqualified	4%

Q.—In your judgment do cinchophen and cinchophen derivatives have any essential therapeutic effect which cannot be accomplished more safely by properly regulated doses of other medicaments?

No	189	No	71%
Yes	63	Yes	24%
Disqualified	14	Disqualified	5%

Q.—Can cinchophen and cinchophen derivatives be administered in therapeutically active doses by physicians or by others with confidence that serious deleterious effects will not supervene?

No	211	No	79%
Yes	34	Yes	13%
Disqualified	21	Disqualified	8%

Q.—Can the pathology of cinchophen poisoning be counteracted or cured by specific measures once the symptoms of poisoning have appeared?

No	205	No	77%
Yes	28	Yes	11%
Disqualified	33	Disqualified	12%

COMMENTS

Should be dispensed only on nonrefillable prescription	4
Could be done without very well	1
Injuries are due to hypersensitivity	5
Should be denied general public except on prescription	27
Use undesirable even by physicians	4
Physicians should be able to get it even though very dangerous	4
Does not use because of reported injuries	4
Particularly useful in the treatment of gout	24
Especially effective in mobilization of uric acid	10
Unsafe in the hands of the average physician	2

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SATURDAY, OCTOBER 4, 1941

TUBERCLE BACILLI IN FASTING GASTRIC CONTENTS

The finding of the tubercle bacillus is of the utmost importance as evidence in the diagnosis of tuberculosis. Tuberculous infants and young children do not expectorate their sputum; they swallow it. Meunier in 1898 examined the fasting gastric contents of tuberculous children by staining the centrifuged gastric specimen. The method did not attract attention until the report by Armand-Delille and Vibert in 1927. In the course of the next nine years Armand-Delille and Kérambrun [1] investigated 1,298 cases of respiratory disease in children by this method. Of these, 712 were exposed to tuberculosis in their homes and manifested signs of pulmonary or lymph node tuberculosis and positive cutaneous reactions. The gastric contents were examined by direct microscopy and in some instances by inoculation into guinea pigs or by the culture method of Loewenstein or of Petragnani. Bacilli were recovered in more than 50 per cent of 668 tuberculous children but in only 3 of 586 children with cough and auscultatory signs, without history of contact and without roentgenographic signs. The method demonstrated the possibility of discovering bacillus carriers in children presenting no more than tracheo-bronchial adenopathy.

Poulsen and his co-workers [2] in Denmark examined 622 tuberculous children and found 199 positive for tubercle bacilli by guinea pig inoculation of gastric contents. The children under 4 years of age were much more frequently positive than older children. By repeating the lavage examination four times, the incidence of positive results was increased from 70 to 97 per cent. Nils Levin [3] of Sweden examined 283 children with active primary tuberculosis and found that 68 per cent had tubercle bacilli in their gastric contents. Only a few were positive on direct smear. He prefers guinea pig inoculation to the culture method because it is a much more sensitive test. In this country Ina Gourley [4] reported the results of studying a series of 210 tuberculous children by means of gastric lavage and guinea pig inoculation. Tubercle bacilli were demonstrated in 84, or 40 per cent; 68 children tuberculin negative to 1.0 mg. were found to be free of tubercle bacilli. The question of infectivity of these children has not thus far been definitely answered. Rosencrantz and Hurwitz [5] demonstrated tubercle bacilli in 76 (45 per cent) of 169 tuberculin positive children by the method of inoculation of the gastric contents in guinea pigs. The younger the group the higher the percentage of positive results up to 5 years, when the percentage decreased.

Stadnichenko and Cohen [6] reported the results of using the method on 600 adult patients admitted to the Chicago Municipal Tuberculosis Sanitarium. Examination of the patients with clinical tuberculosis who had never shown a positive sputum revealed the presence of tubercle bacilli in 46 per cent when gastric sediment was injected in guinea pigs; 39 per cent of these were positive in smears. These authors believe that better results are obtained by injecting untreated gastric contents. Of their patients with a diagnosis of freedom from tuberculosis, 130 were found to have both sputum and gastric washings negative for tubercle bacilli. They conclude that the incidence of a false positive reaction is remote and that the presence of tubercle bacilli in the gastric sediment indicates that the patient has active pulmonary tuberculosis. By the addition of gastric lavage to examinations of sputum, Roper and Ordway [7] increased the recovery of tubercle bacilli from 34.8 per cent to 69.1 per cent in 123 adult tuberculous patients. There were 36 patients who either did not expectorate or were producing sputum which was consistently negative by microscopic examination and animal inoculation. Lavage of the stomach yielded positive results in all of these. The presence or absence of bile in the gastric specimen was without significant influence on the results of animal inoculation. The viability of virulent tubercle bacilli was likewise not affected by free hydrochloric acid up to tenth-normal strength even after forty hours of exposure. Of 90 patients who did not exhibit roentgenologic signs of tuberculous enterocolitis, 43 were positive. It therefore appears that regurgitation from the intestine into the stomach of bacilli from tuberculous lesions in the intestine is highly improbable.

Inoculation into guinea pigs of centrifuged fasting gastric contents is undoubtedly the most sensitive method for the diagnosis of pulmonary tuberculosis.

1. Armand-Delille, P. F., and Kérambrun: La recherche du bacille tuberculeux dans l'estomac. Sa valeur diagnostique. Résultats de cette investigation chez 1,298 enfants atteints, Bull. Acad. méd. **115**: 467 (March 17) 1936.

2. Poulsen, Valdemar, and Anderson, A. O.: Four Years' Experience with Examination of Material Obtained by Gastric Lavage, Am. J. Dis. Child. **47**: 307 (Feb.) 1934.

3. Levin, Nils: On the Demonstration of Tubercle Bacilli by Means of Lavage of the Stomach in Different Forms of Tuberculosis in Children, Acta paediat. **17** (supp. 1): 160, 1935.

4. Gourley, Ina: Search for Tubercle Bacilli in the Gastric Contents of Tuberculous and Nontuberculous Children, National Tuberculosis Association, 33d annual meeting 1937, p. 131.

5. Rosencrantz, Esther, and Hurwitz, Samuel: Guinea Pig Inoculation with the Gastric Contents of Tuberculous Children, Am. Rev. Tuberc. **41**: 645 (May) 1940.

6. Stadnichenko, Asya, and Cohen, S. J.: Gastric Lavage as a Means of Demonstrating Tubercle Bacilli in Pulmonary Tuberculosis, National Tuberculosis Association, 33d annual meeting, 1937, p. 125.

7. Roper, W. H., and Ordway, W. H.: Gastric Lavage in Adults with Pulmonary Tuberculosis, Am. Rev. Tuberc. **43**: 543 (April) 1941.

CAROTID SINUS SYNCOPE

In recent years experimental investigations have demonstrated that the regulation of blood pressure is fundamentally an automatic, proprioceptive, reflex mechanism. The endovascular pressure itself regulates and automatically adapts the cardiac output, the circulating blood volume and the peripheral vascular resistance so well that the arterial pressure is maintained within normal limits. This automatic and proprioceptive regulation is effected mainly by the intermediation of the pressoreceptor innervation of different arterial and venous vascular areas. Knowledge of the role of the carotid sinus reflex in regulating and controlling the endovascular blood pressure is due chiefly to the researches of Hering.[1] In 1923 he demonstrated that the same degree of slowing of the heart rate took place in animals when mechanical pressure was applied directly to the bifurcation of the common carotid artery even after the vagus was separated from the artery. Thus Czermak's explanation of the effect of pressure on the vagus was proved to be incorrect. The researches of Hering, of Heymans [2] and of de Castro demonstrated that the dilated portion of the bifurcation of the common carotid artery is richly supplied with sensory receptors which originate in the adventitia and leave the sinus as the sinus nerve of Hering or the intercarotid nerve of de Castro to join the glossopharyngeal nerve. Thus afferent direct nerve connection exists between the carotid sinus and the medullary centers. Hering demonstrated in animal experiments that variation of localized mechanical pressure within the carotid sinus produced prompt changes in the systemic arterial pressure and the heart rate. The afferent portion of this regulatory reflex, located in the nerve structures of the carotid sinus, carries impulses to the central nervous system, which in turn, through efferent channels, the vagus or the cervical sympathetics, induces peripheral vasodilatation, slowing of the heart and fall in the arterial pressure, if the pressure within the sinus is raised; and vasoconstriction, increased heart rate and rise in blood pressure, if the intrasinal pressure is lowered. Hering and Koch stipulated that "increase in the intrasinal pressure gives rise to active tonic respiratory impulses, while a decrease in pressure causes these afferent impulses to subside and the medullary centers to overact." Heymans [2] demonstrated that the continuous secretion of epinephrine is reflexly controlled by the afferent, aortic and sinus nerves. In the carotid sinus, therefore, we have an example of a nervous mechanism which controls the circulation not only directly but also indirectly through chemical regulation.

Koch studied the effect of pressure over the carotid sinus of 50 unselected persons. In 28 instances the test resulted in a fall in the systolic pressure averaging 23 per cent of the initial level. Mandelstamm and Lifschitz [3] succeeded in inducing a fall in systolic pressure of at least 10 mm. of mercury in 60 per cent of 335 cases. The degree of fall was particularly pronounced in cases of arteriosclerosis and hypertension. They concluded that stimulation of the sinus nerve in man results in a true depressor nerve reflex. Weiss and Baker [4] found that mechanical stimulation of the carotid sinus of 50 normal subjects produced either no fall in the systemic blood pressure or a fall of less than 10 mm. of mercury. In 42 cases of arterial hypertension and in 36 cases of primary arteriosclerosis but without hypertension the fall in arterial pressure occurred more frequently and was of greater degree. These authors conducted a study on 15 persons in whom the carotid sinus reflex was hyperactive. Thirteen of these complained of spontaneous dizziness and fainting attacks, and pressure on one of the sinuses induced dizziness and fainting together with convulsive seizures. In 4 cases a sudden turn of the head induced dizziness and fainting. In 6 there was aneurysmal dilatation of one or both sinuses and in 3 a small tumor pressing on the sinus. However, in the remaining 6 cases no gross abnormality was present.

Three main types of cardiovascular response were observed: (*a*) vagal, characterized by marked asystole or sudden slowing of the heart rate, with or without marked fall in the arterial blood pressure; (*b*) depressor, characterized by well defined fall in the arterial blood pressure, without essential cardiac slowing, and (*c*) cerebral, due to changes in cerebral circulation, without essential slowing of the heart rate and without fall in the arterial blood pressure, and characterized by paling of the face, followed by intense flushing.

Ferris, Capps and Weiss [5] report observations on 32 patients who suffered from spontaneous attacks of dizziness, weakness and unconsciousness, with or without convulsions, and in whom mechanical stimulation of the carotid sinus promptly induced manifestations of identical nature. They have subjected 7 of the patients to surgical denervation of the sensitive carotid sinus. Complete cure of the spontaneous attacks has been obtained to date in every case. These authors feel that therapeutic denervation of the carotid sinus should include portions of the external, internal and common carotid arteries. They conclude that manifestations of the hyperactive carotid sinus reflex are the result of abnormalities in portions of the autonomic nervous system rather than of the entire system.

1. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe vom normal-physiologischen, pathologisch-physiologischen und klinischen Standpunkt, Dresden, Theodor Steinkopff, 1927.

2. Heymans, Corneille: The Pressoreceptive Mechanisms for the Regulation of Heart Rate, Vasomotor Tone, Blood Pressure and Blood Supply, New England J. Med. **219:** 147 (Aug. 4) 1938.

3. Mandelstamm, M., and Lifschitz, S.: Die Wirkung der Karotissinusreflexe auf den Blutdruck beim Menschen, Wien. Arch. f. inn. Med. **22:** 397 (July) 1932.

4. Weiss, Soma, and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Role in the Causation of Fainting and Convulsions, Medicine **12:** 297 (Sept.) 1933.

5. Ferris, E. B., Jr.; Capps, R. B., and Weiss, Soma: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions: A Study of Thirty-Two Additional Cases, Medicine **14:** 377 (Dec.) 1935.

That stimulation of the carotid sinus in the presence of an advanced cerebral arteriosclerosis is not without danger is suggested by the case of Marmor and Sapirstein [6] in which stimulation of the right carotid sinus, in the course of an examination, induced immediately a carotid sinus syncope followed by a progressive thrombosis of both anterior cerebral arteries ending fatally.

Craig and Smith [7] believe that, when the symptoms are mild and the attacks infrequent, reassurance alone will suffice. When the symptoms are more severe, the patient is to be instructed to avoid turning his head quickly, looking upward and stooping suddenly. He should avoid any constriction about the neck. In their experience, medicinal treatment consisting of administration of phenobarbital, ephedrine, amphetamine, atropine and phenytoin has not been satisfactory. When the attacks are severe and the medical treatment has not been successful, denervation of the sensitive sinus is to be recommended. They have performed denervation in 12 cases and report four excellent results, one good result, four fairly good results and three failures. Mulholland and Rovenstine [8] emphasize the importance of determination of the type of the syndrome for the preoperative care and the choice of anesthesia. They have denervated one carotid sinus in each of 5 patients with symptoms of dizziness and fainting brought on spontaneously or by pressure in the region of the sinus. All the patients were completely relieved of this complaint. Certainly denervation of the sensitive carotid sinus appears justified in properly selected instances.

6. Marmor, Judah, and Sapirstein, M. R.: Bilateral Thrombosis of Anterior Cerebral Artery Following Stimulation of a Hyperactive Carotid Sinus, J. A. M. A. **117**: 1089 (Sept. 27) 1941.

7. Craig, W. McK., and Smith, H. L.: The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes: Report of Thirteen Cases, Yale J. Biol. & Med. **11**: 415 (May) 1939.

8. Mulholland, J. H., and Rovenstine, E. A.: Surgery in the Carotid Sinus Syndrome, Surgery **9**: 751 (May) 1941.

Current Comment

BIOPSY

Language is constantly changing. The sense of a word in common usage may diverge so far from the dictionary definition that redefinition may be required. Consider the word "biopsy." The dictionaries agree essentially in defining biopsy as the examination for purposes of diagnosis of a portion of tissue removed from the living body. Usage, however, seems to make "biopsy" mean the process of removing the living tissue rather than the examination. If the dictionaries are followed, the procedure of removal is described in such a roundabout manner as "removal of lymph node for biopsy." If common usage is followed and the word is employed to refer to the procedure of removal only, the examination is awkwardly described as "examination of tissue removed by biopsy." Etymologically the term "biopsy" must be compared with the words "necropsy" or "autopsy," which mean examination of the dead body; the dictionary definition is correct etymologically in restricting the definition to the examination. Practically, however, the removal of tissue and its examination are integral parts of the same procedure; ordinarily the entire process, including both removal and examination, is meant when the word "biopsy" is employed. The following working definition will be followed in the future in the use of the word "biopsy" in publications of the American Medical Association: "The removal and examination of a piece of tissue from the living body for purposes of diagnosis (usually microscopic)." For example, the phrase "biopsy of lymph node" will mean the procedure of removal and examination, and "the biopsy showed . . ." will refer to the results of the examination as part of the whole procedure.

DENTAL STATUS OF YOUNG MEN OF MILITARY AGE

Faulty and defective teeth head the list as the greatest single cause of deferment [1] under the Selective Service Act. Klein [2] studied several hundred men, including some enrolled in National Youth Administration projects and others attending a national defense training school. Of 642 men between the ages of 21 and 35 years 97 would be rejectable for full military service according to Selective Service dental requirements,[3] while the remainder would be acceptable. The rejectable men were found to have an average of twenty-two permanent teeth attacked by caries. (It is pertinent to note that in this survey decayed, missing and filled teeth are considered to have been attacked by caries.) Of the twenty-two teeth having caries experience, thirteen are already extracted, two need to be extracted, two have been filled and five are carious and justify treatment by fillings. As pointed out by Klein, the teeth of the rejectable men clearly have a more pronounced tendency to be attacked by caries than those of the acceptable individuals. Both acceptable as well as rejectable men needed dental care. Indeed, in Klein's report is found the rather startling and thought provoking conclusion that in the group surveyed nine out of ten of the rejectable men needed full or partial dentures, and the same proportion of the acceptable men needed partial dentures or bridges. Until dental caries can be prevented, the excessive accumulation of need for fillings, dentures and bridges can be obviated by systematic, perennial dental servicing, beginning in the first decade of life and continuing without interruption through the late adult ages.

1. Britten, R. H., and Perrott, G. S.: Causes of Physical Disqualification Under the Selective Service Law: Early Indications, Pub. Health Rep. **56**: 1017 (May 9) 1941. Physical Disqualification Under the Selective Service Law, Current Comment, J. A. M. A. **117**: 114 (July 12) 1941.

2. Klein, Henry: The Dental Status and Dental Needs of Young Adult Males Rejectable or Acceptable for Military Service According to Selective Service Dental Requirements, Pub. Health. Rep. **56**: 1369 (July 4) 1941.

3. According to the U. S. War Department Mobilization Regulations MR1-9, issued Aug. 31, 1940, an individual to be placed in class I-A must have a minimum of three serviceable natural masticating teeth (including molars and biscupids) above and three below opposing, and three serviceable natural "incisors" (including incisors and cuspid teeth) above and three below opposing. All the teeth must be so opposed as to serve the purpose of incision and mastication. Class I-B includes individuals whose teeth have been corrected by suitable dentures but who have insufficient teeth to qualify for class I-A. Klein.[2]

MEDICAL PREPAREDNESS

In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.

ARMY TUBERCULOSIS RATE IS LOWEST IN FOUR YEARS

Data available to the Army Medical Department indicate that the rate of tuberculosis in the Army for the first six months of 1941 was 0.85 per thousand men, a figure that compares favorably with the rate prevalent before the Army was expanded under the national defense program, the War Department has announced. This low figure is attributed to the measures being taken to detect this pulmonary disease before men are accepted for service by Army induction boards and to the high health standards maintained in the Army. The War Department has directed that all men sent to Army induction stations by local boards must receive roentgen examinations of the chest. It is now possible to give roentgen examinations to all trainees in the first, second, third, sixth and eighth corps areas. By the end of the year, as equipment and professional personnel are available, every man will receive the roentgen examination before he is accepted for service in the Army. Even where facilities do not exist now to examine every man, a roentgen examination is ordered for any man in whom there appears any suggestive history of pulmonary disease.

PROMOTION OF RESERVE OFFICERS

The War Department announced, August 25, the following instructions governing the permanent and temporary promotions of reserve officers:

1. Colonels and lieutenant colonels: Effective at once, the promotions of all reserve officers to the rank of colonel and lieutenant colonel are suspended until further notice.

2. Not on extended active duty: Effective at once, promotions of all reserve officers not on extended active duty, excepting only those officers who have been returned to an inactive status following satisfactory performance of twelve consecutive months' extended active duty and who meet the requirements of paragraph 31, AR 140-5, are suspended until further notice. Active duty with the CCC will not be considered for this purpose.

3. Permanent promotions: on extended active duty. Reserve officers on extended active duty may be granted permanent promotions to and including the rank of major, under these conditions:

(*a*) Have obtained a certificate of capacity and completed time in grade as prescribed in paragraph 31, AR 140-5, June 17, 1941. Vacancies under the peacetime procurement objective are not required.
(*b*) Have served six months or more on their current tour of extended active duty.
(*c*) Appropriate vacancies or assignments exist with the Army, War Department Overhead, or Corps Area Service Command, in which serving.
(*d*) Action toward promotion must originate with the officer's unit commander and be forwarded to the War Department through command channels.

4. Temporary promotions: on extended active duty. Temporary promotions are authorized for qualified officers of the following categories, with service on Aug. 1, 1941 as indicated. The service need not be consecutive:

(*a*) First lieutenants, permanent or temporary, of promotion list branches, including Medical Administrative Corps, with three years' extended active duty (not necessarily in grade).
(*b*) First lieutenants of nonpromotion list branches (chaplains and Medical Department less Medical Administrative) with one year's extended active duty.
(*c*) All second lieutenants with one year's extended active duty.
(*d*) Active duty with the CCC will be excluded in computing the foregoing extended active duty.

5. Recommendations: The names of all reserve officers of the categories listed in paragraph 4 who are considered qualified for and are recommended for promotion to the next higher grade will be reported to the War Department so as to reach this office not later than Oct. 1, 1941. In order to preserve the present seniority in grade of officers recommended for promotion, all acceptances will be accomplished on a date to be announced later. Unit commanders and heads of sections of War Department overhead and of the corps area service command are charged with the responsibility for initiating such action as will insure that only qualified officers on extended active duty are recommended.

6. All regulations or instructions in conflict with the foregoing are suspended.

TEN THOUSAND NURSES NEEDED FOR THE ARMY

More than ten thousand nurses are needed for the Army Nurse Corps, the War Department announced September 18. Surgeon General of the Army Major Gen. James C. Magee said that 5,973 nurses are now on duty but that to meet the authorized quota 2,264 more are needed. This figure includes 526 additional Regular Army nurses and 1,738 reserve nurses. An additional 4,000 reserve nurses will be needed to care for trainees to be inducted into the Army this year.

The Army Nurse Corps anticipates that 40 per cent of reserve nurses who had accepted one year's assignment will request discharge at the expiration of their twelve months' service. As a result, 4,144 reserve nurses over the authorized quota must be enrolled to balance the number of retiring nurses. The total number of nurses needed comes to 10,408.

To become a Regular Army nurse, the applicant must be between 22 and 30 years of age, unmarried and a citizen of the United States. She must meet the physical requirements for Army nurses and must be a graduate of an accredited high school, a school of nursing of approved standards and also be a registered nurse.

To become a reserve nurse, the applicant must be between 21 and 40 years of age, unmarried, a citizen of the United States and physically fit. She must be a high school graduate and a graduate of an approved school of nursing connected with a hospital giving a three years course in basic nursing subjects. The hospital must have had a daily average of at least 50 patients and must have had separate departments. A reserve nurse goes on active duty almost immediately after she is sworn in as an Army nurse and remains on duty for at least a year, unless discharged sooner. When a reserve nurse is discharged she ceases to be a member of the Army Nurse Corps. There are no Army reserve nurses on the inactive list.

The initial pay of an Army nurse is $840 a year plus maintenance. The salary increases with length of service and the pay after nine years of service is $1,560 a year plus maintenance. The new Army nurse receives the grade of Nurse, with the relative rank of Second Lieutenant. In addition to the white duty uniforms, nurses have a two tone, blue covert cloth uniform with maroon trimmings, and a blue cape.

For information on a career as a Regular Army nurse, an applicant should write the Surgeon General of the Army, War Department, Washington, D. C. For information on becoming a reserve nurse, inquiry should be made at the headquarters of the American Red Cross in Washington, D. C.

EXAMINATIONS FOR APPOINTMENT IN THE NAVY MEDICAL CORPS

The Navy Department has announced that three examinations have been scheduled for candidates for appointment in the Medical Corps of the U. S. Navy as assistant surgeons and acting assistant surgeons for intern training.

Examinations for appointment as assistant surgeon with the permanent rank of lieutenant (junior grade) are listed for October 6 to October 9 inclusive and for Jan. 5 to Jan. 9, 1942 inclusive, while those for acting assistant surgeon with the probationary rank of lieutenant (junior grade) are set for January 5 to January 9 inclusive.

Applicants for appointment as assistant surgeon are required to be citizens of the United States of over 21 but less than 32 years of age at time of acceptance of commissioning, graduates of class A medical schools, to have had at least one year of intern training in a hospital accredited for intern training by the Council on Medical Education and Hospitals of the American Medical Association and to meet the physical and other requirements for appointment.

Those applying for appointment as acting assistant surgeon for intern training are required to be citizens of the United States of over 21 but less than 32 years of age, members of the junior or senior classes in class A medical schools and to meet the physical and other requirements for appointment.

Acting assistant surgeons for intern training are assigned in U. S. naval hospitals which have been accredited for intern training by the Council on Medical Education and Hospitals of the American Medical Association and after they have completed twelve months of intern training may, if they so desire, apply for appointment as assistant surgeon in the regular Navy.

Applications for authorization to take the examinations must be in the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., three weeks prior to the date of the examination. Application forms for these examinations will be forwarded by that bureau on request.

A circular of information which contains full information regarding physical requirements, professional examination, rates of pay and promotion and retirement date may be obtained by addressing the Bureau of Medicine and Surgery, Navy Department, Washington, D. C.

REEXAMINATION OF DRAFTEES WHO FAILED

A statewide so-called superselective service medical advisory board has been organized in Illinois comprising about four hundred medical specialists, which will have as its principal function the reexamination of draft registrants who have failed to qualify physically for military service since the draft law went into effect. The purpose is to determine whether any of such registrants can now be placed in class 1-A for immediate army duty and also to endeavor to rehabilitate such cases as may be corrected. The chairman of this board is Dr. Irving S. Cutter, dean emeritus of Northwestern University Medical School, Chicago. The tuberculosis division will be headed by Dr. Frederick Tice, Chicago, and the venereal disease division by Dr. Herman N. Bundesen, Chicago, commissioner of health. According to Major E. Mann Hartlett, state draft medical director, there will be other divisions of the committee's work, such as the heart and circulatory division, and the dental division.

ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

FIRST CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, First Corps Area, which comprises the states of Maine, Vermont, New Hampshire, Rhode Island, Massachusetts and Connecticut:

BEGG, Charles F., 1st Lieut., Providence, R. I., Camp Edwards, Mass.
BOYD, Phillips L., Major, Jamaica Plain, Mass., Boston University, Boston.
CAREY, Francis G., 1st Lieut., Dorchester, Mass., Fort Devens, Mass.
DORSEY, Joseph F., 1st Lieut., Boston, Camp Lee, Va.
DROBNES, Sidney, 1st Lieut., Norwich, Conn., Camp Lee, Va.
FABRICANT, Milton W., 1st Lieut., New London, Conn., Fort H. W. Wright, N. Y.
GROVER, Morris L., Captain, Providence, R. I., Fort George G. Meade, Md.
HARVEY, Harold I., 1st Lieut., New Britain, Conn., Camp Edwards, Mass.
JENNES, Milton L., 1st Lieut., Waterbury, Conn., Camp Edwards, Mass.
KRONICK, Macey, 1st Lieut., Greenfield, Mass., Camp Lee, Va.
LEVIN, Aaron H., 1st Lieut., Brookline, Mass., Camp Lee, Va.
McDONOUGH, Walter J., 1st Lieut., Dorchester, Mass., Fort Devens, Mass.
RICHER, Arthur G., 1st Lieut., Marlboro, Mass., Camp Lee, Va.
RUSSO, Edward A., 1st Lieut., Boston, Fort Adams, R. I.
SABIN, George M., 1st Lieut., Burlington, Vt., Fort Ethan Allen, Vt.
SEIGAL, Harold L., 1st Lieut., Boston, Fort Devens, Mass.
VEZINA, Raoul E., 1st Lieut., Springfield, Mass., Camp Edwards, Mass.
WEINBERG, Julius, 1st Lieut., Concord, N. H., Fort Banks, Mass.

Orders Revoked

BARCOMB, Albert E., 1st Lieut., Rochester, N. H.
BARRETT, Charles G., Captain, Amherst, Mass.
FERRARA, Bernardino F., 1st Lieut., Providence, R. I.
GLADSTONE, Robert W., 1st Lieut., Pittsfield, Mass.
GLENN, William W. L., 1st Lieut., Boston.
MILLER, George F., 1st Lieut., Dorchester, Mass.
POPOFF, Constantine, Lieut-Col., Haverhill, Mass.
SANDER, Hermann N., 1st Lieut., Manchester, N. H.
VALENSKI, Thaddeus J., 1st Lieut., Thompsonville, Conn.

SECOND CORPS AREA

The following additional medical reserve corps officers have been ordered to active duty by the Commanding General, Second Corps Area, which comprises the states of New York, New Jersey and Delaware:

BERADI, Luke J., 1st Lieut., Mount Vernon, N. Y., Camp Polk, La.
BOTTINO, Clement G., 1st Lieut., New York, Fort Dix, N. J.
BRAY, Harold P., 1st Lieut., Long Island City, N. Y., Fort Knox, Ky.
BREED, James R., 1st Lieut., Wappinger Falls, N. Y., Northern New Jersey Recruiting District, Newark, N. J.
BRUMBERGER, Gustave, 1st Lieut., St. Albans, N. Y., Pine Camp, N. Y.
CALABRESE, Dino D., 1st Lieut., Fort Lee, N. J., Fort Knox, Ky.
GAGLIARDI, Francis A., 1st Lieut., Richmond Hills, N. Y., Camp Polk, La.
GOLDSTEIN, Edward W., 1st Lieut., Paterson, N. J., Fort Knox, Ky.
HOGAN, Raymond L., 1st Lieut., Brooklyn, Fort DuPont, Del.
HOWARD, Weaver O., 1st Lieut., Camp May, N. J., Fort Dix, N. J.
JACOBS, Thomas P., 1st Lieut., New Rochelle, N. Y., Camp Polk, La.
KASS, Albert, 1st Lieut., New York, Camp Polk, La.
KATZENSTEIN, Kurt H., 1st Lieut., New York, Camp Polk, La.
LAURUSONIS, John J., 1st Lieut., Paulsboro, N. J., Camp Polk, La.
LOBES, Louis A., 1st Lieut., Mount Vernon, N. Y., Fort Ethan Allen, Vt.
MAR, Thomas M., 1st Lieut., Wechawken, N. J., Fort Knox, Ky.
PELLECCHIA, Leonard J., 1st Lieut., Newark, N. J., Fort Knox, Ky.
PHILLIES, Eustace G., 1st Lieut., Buffalo, Fort Dix, N. J.
RIBAUDO, Salvatore J., 1st Lieut., Brooklyn, Camp Polk, La.
SCHECHTER, Milton, 1st Lieut., New York, Camp Polk, La.
SHEEHY, James E., 1st Lieut., Brooklyn, Pine Camp, N. Y.
SINGER, Leon, 1st Lieut., New York, Fort Knox, Ky.
TABER, Frederick S., Captain, New Brunswick, N. J.
VILARDO, William, 1st Lieut., Garfield, N. J., Fort Knox, Ky.
YETZER, William J., 1st Lieut., Buffalo, Fort Knox, Ky.
ZIGARELLI, Joseph F., 1st Lieut., Paterson, N. J., Fort Knox, Ky.

THIRD CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, Third Corps Area, which comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland:

ALPERN, Samuel, 1st Lieut., Pittsburgh, Camp Polk, La.
BRICE, Gratien Bertrand, 1st Lieut., Titusville, Pa., Camp Lee, Va.
BROMMER, Oliver Raymond, 1st Lieut., Philadelphia, Camp Lee, Va.
CARP, Leon Moses, 1st Lieut., Philadelphia, Fort Bragg, N. C.
COLLINS, Clyde Abraham, 1st Lieut., Scranton, Pa., Fort Eustis, Va.
COSTELLO, Robert Francis, 1st Lieut., Washington, D. C., Camp Lee, Va.
DALRYMPLE, Richard Young, 1st Lieut., Hanover, Pa., Fort Story, Va.
FULTZ, George Simeon, Jr., 1st Lieut., Butterworth, Va., Fort Bragg, N. C.
FURST, William, 1st Lieut., Philadelphia, Indiantown Gap Military Reservation, Pa.
GREENFIELD, Alfred Robert, 1st Lieut., McKeesport, Pa., Camp Lee, Va.
HAWKINS, Sumpter Wright, 1st Lieut., Abington, Pa., Fort George G. Meade, Md.
HEIM, Hugh Wilson, 1st Lieut., Schuylkill Haven, Pa., Camp Lee, Va.
HENDERSON, Jonathan Kearsley, 1st Lieut., Philipsburg, Pa., Camp Lee, Va.
HUNTER, John Sidney, 1st Lieut., West Reading, Pa., Camp Lee, Va.
JAMES, Charles Fleetwood, Jr., 1st Lieut., Appomattox, Va., Fort Monroe, Va.
KATZ, Albert Herbert, 1st Lieut., Sharpsburg, Pa., Fort Jackson, S. C.
KROHN, Harold Allen, 1st Lieut., Lebanon, Pa., Camp Lee, Va.
LIEBERMAN, George Emanuel, 1st Lieut., Philadelphia, Fort George G. Meade, Md.
MARTYAK, Gabriel Stephen, 1st Lieut., Hazleton, Pa., Camp Lee, Va.
MITCHELL, Edward Albert, 1st Lieut., Clinchco, Va., Camp Lee, Va.
MITTERLING, Robert Carl, 1st Lieut., Philadelphia, Headquarters 3d Corps Area, Baltimore.
O'BRIEN, Clyde Garvice, 1st Lieut., Appomattox, Va., Fort Story, Va.
PROKOP, Albert George, 1st Lieut., Clairton, Pa., Camp Lee, Va.
ROBINSON, William Herbert, III, 1st Lieut., Roaring Springs, Pa., Camp Lee, Va.
SCHROEDER, Alfred R., 1st Lieut., Washington, D. C., Fort Belvoir, Va.
SCHWARTZ, John Meese, 1st Lieut., East McKeesport, Pa., Indiantown Gay Military Reservation, Pa.
SHULMAN, Leon Meyer, 1st Lieut., Baltimore, Camp Livingston, La.
SNYDER, Gordon Elias, 1st Lieut., New Milford, Pa., Fort George G. Meade, Md.
SPOSATO, Emil, 1st Lieut., Washington, Pa., New Cumberland, Pa.
THOMAS, Arthur Benjamin, Captain, Pittsburgh, Aberdeen Proving Ground, Md.
THOMAS, Henry William, 1st Lieut., Pittsburgh, Fort Belvoir, Va.
WOLFE, Joseph David, 1st Lieut., Bessemer, Pa., Fort Belvoir, Va.

Orders Revoked

GRATZ, Morton M., 1st Lieut., Appomattox, Va.
HENDERSON, Jonathan Kearsley, 1st Lieut., Philipsburg, Pa.
ROBINSON, William Herbert, III, 1st Lieut., Roaring Spring, Pa.
SCHEIE, Harold Glendon, Captain, Philadelphia.
TISHERMAN, Robert Carl, Captain, Pittsburgh.
TODD, Oswald Valentine, 1st Lieut., Washington, D. C.

FIFTH CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, Fifth Corps Area, which comprises the states of Ohio, West Virginia, Indiana and Kentucky:

APPEL, William, 1st Lieut., Fort Wayne, Ind., Camp Shelby, Miss.
BINZER, Isadore I., 1st Lieut., Toledo, Ohio, Fort Knox, Ky.
DiCELLO, Anthony J., 1st Lieut., Elkins, W. Va., Fort Knox, Ky.
GILBERT, Harold R., 1st Lieut., Cleveland, Fort Knox, Ky.
HORTON, Robert J. M., 1st Lieut., Cleveland Heights, Ohio, Fort Knox, Ky.
KABEL, Robert N., 1st Lieut., Indianapolis, Fort Knox, Ky.
KIRCHMAN, Herbert, 1st Lieut., Germantown, Ohio, Fort Hayes, Ohio.
McCLELLAND, Harry N., 1st Lieut., Indianapolis, Fort Knox, Ky.
PENNINGTON, Clarke P., 1st Lieut., Louisville, Ky., Fort Hayes, Ohio.
STEMPIEN, Stephen J., 1st Lieut., Cleveland Heights, Ohio, Fort Hayes, Ohio.
TROCKMAN, Richard J., 1st Lieut., Evansville, Ind., Camp Shelby, Miss.
WEINBLATT, Morris, 1st Lieut., Toledo, Ohio, Fort Hayes, Ohio.
WOOD, Benjamin J., 1st Lieut., Cleveland, Fort Thomas, Ky.

CORRECTION

Lieutenant Glasser.—In THE JOURNAL, August 16, in the Medical Preparedness section, under the Fifth Corps Area, the name of First Lieut. Seymour Blasser, Outwood, Ky., was misspelled and should have been First Lieut. Seymour Glasser.

NINTH CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, Ninth Corps Area, which comprises the states of Washington, Montana, Oregon, Nevada, Utah, California and Idaho:

BALCH, Harry E., 1st Lieut., Alhambra, Calif., Kodiak, Alaska.
BURNIGHT, Ernest R., Captain, Marysville, Calif., Camp San Luis Obispo, Calif.
CLANTON, Edward L., 1st Lieut., Rockford, Wash., Corps Area Service Command, Unit 1907, Fort Lewis, Wash.
CLOTHIER, William L., 1st Lieut., Los Angeles, Camp Callan, Calif.
CRAGIN, Robert Brower, Major, San Jose, Calif., 183d Field Artillery, Fort Francis E. Warren, Wyo.
EDWARDS, James S., 1st Lieut., Salt Lake City, 3d Division, Fort Lewis, Wash.
EGLESTON, E. Francis, 1st Lieut., San Francisco, 3d Division, Fort Lewis, Wash.
GENTLE, Hjalmar T., Captain, Medford, Ore., Corps Area Service Command, Unit 1907, Fort Lewis, Wash.
JACOBUS, Willis L., Jr., 1st Lieut., Los Angeles, Camp Haan, Calif.
JETTON, James A., Captain, Fallbrook, Calif., 11th Cavalry, Camp Seeley, Calif.
MAHER, Edward J., 1st Lieut., San Jose, Calif., Fort Ord, Calif.
McINTYRE, Harold E., 1st Lieut., Billings, Mont., Corps Area Service Command, Unit 1907, Fort Lewis, Wash.
MISRACK, Maury L., 1st Lieut., San Francisco, Camp San Luis Obispo, Calif.
MOORE, Herbert L., 1st Lieut., Eureka, Calif., Fort Ord, Calif.
O'NEILL, Thomas J., 1st Lieut., Los Angeles, Fort Rosecrans, Calif.
PORTER, James L., 1st Lieut., National City, Calif., 250th Coast Artillery, Camp McQuaide, Calif.
RILEY, William H., Captain, Fresno, Calif., Corps Area Service Command, Unit 1962, Fort Ord, Calif.
SCHADE, George H., 1st Lieut., San Francisco, Camp Haan, Calif.
VASKO, John R., Captain, Great Falls, Mont., 3d Division, Fort Lewis, Wash.
WOLF, Clare C., 1st Lieut., Sumner, Wash., Corps Area Service Command, Unit 1907, Fort Lewis, Wash.
WOOD, Clarence L., 1st Lieut., St. Helena, Calif., 3d Army Corps, Presidio of Monterey, Calif.
WYLIE, Charles R., 1st Lieut., Los Angeles, 57th Medical Battalion, Fort Ord, Calif.
ZIEGLER, Elmer F., 1st Lieut., Sacramento, Calif., Fort Ord, Calif.

Relieved from Active Duty

BOLSTAD, Donald S., 1st Lieut., Fort Richardson, Alaska.
CARLQUIST, John H., 1st Lieut., Camp Roberts, Calif.
DAVENPORT, Donald J., 1st Lieut., Presidio of Monterey, Calif.
JOHNSON, Arthur F., 1st Lieut., Fort Lewis, Wash.
KYLE, Charles L., Captain, Camp Murray, Wash.
MAYER, Leo L., 1st Lieut., Camp Callan, Calif.
WHITE, Almon J., 1st Lieut., 9th Army Corps, Fort Lewis, Wash.

NAVY DEPARTMENT

The Navy Department, September 20, announced the following changes of duty:

ALLEN, Abraham H., Captain, from Navy Yard, Philadelphia, to Fourth Naval District, for duty as District Medical Officer of that district.
BROWN, Ernest W., Captain, from Navy Yard, Brooklyn, to Bureau of Medicine and Surgery, Navy Department, Washington, D. C.
KAUFMAN, John B., Captain, from Fourth Naval District, to retire.
RAISON, Thomas W., Captain, from Destroyer Base, San Diego, Calif., to Medical Officer in Command, Naval Dispensary, Long Beach, Calif.
RIORDAN, John F., Captain, from Medical Officer in Command, Naval Dispensary, Long Beach, Calif., to Fourth Naval District, Philadelphia, for duty at Navy Yard.
THOMAS, Griffith E., Captain, from Eleventh Naval District to Eleventh Naval District for duty at Destroyer Base, San Diego, Calif.
WOOD, Carleton I., Captain, from Naval Dispensary, Long Beach, Calif., to Third Naval District, New York.

ORGANIZATION SECTION

OFFICIAL NOTES

ABSTRACT OF MINUTES OF MEETINGS OF BOARD OF TRUSTEES SEPT. 18 AND 19, 1941

A two day session of the Board of Trustees was held at the headquarters of the Association, September 18 and 19, preceded by a full day meeting of the Executive Committee.

RULES FOR AMERICAN HEALTH RESORTS

Rules proposed by the Committee on American Health Resorts, with the primary object of identifying for the medical profession and the public those health resorts which are shown by investigation of their location, climate, personnel and management to merit recognition by the medical profession were adopted after slight modification of the wording.

DR. THEODORE G. KLUMPP ASSUMES DUTY IN COUNCIL ON PHARMACY AND CHEMISTRY

Dr. Theodore G. Klumpp reported for duty on July 1 as Secretary of the Council on Pharmacy and Chemistry and Director of the Division of Foods, Drugs and Physical Therapy.

IMPROVEMENT IN QUALITY OF AMERICAN DIETS

The Board approved—subject to amendment—a communication to be sent by the Committee on Food and Nutrition of the National Research Council to the physicians of the United States in an effort to improve the quality of American diets.

APPOINTMENTS

Dr. Frederic E. Sondern, New York, to succeed Dr. Alexander Lambert on the Supervisory Board of the American Year Book; Dr. C. A. Elvehjem, Madison, Wis., to succeed Dr. Mary Swartz Rose on the Council on Foods and Nutrition; Dr. Percival Bailey, Chicago, to the Editorial Board of the *Archives of Neurology and Psychiatry;* Dr. Theodore G. Klumpp as member of the United States Pharmacopeial Sterile Products Advisory Board.

VOLUME THREE "MEDICOLEGAL CASES" TO BE PUBLISHED

Authorization was given for the publication in book form of the third series of Medicolegal Cases.

APPROPRIATIONS

Appropriations were made for special exhibits on fractures, lame backs and home and hospital delivery in obstetrics at the Atlantic City session in 1942.

PRIMER ON PHYSICAL THERAPY

Authorization was given for issuing in book form material on physical therapy to be used in army hospitals, which has been prepared by the Council on Physical Therapy and approved by a special committee on physical therapy of the National Research Council.

HOTELS FOR HOUSE OF DELEGATES IN ATLANTIC CITY

The Board selected the Hotel Traymore for the meetings of the House of Delegates in Atlantic City in 1942.

ONLY GRADUATES OF MEDICAL SCHOOLS WITH M.D. DEGREE OR ITS EQUIVALENT AND PHYSICIANS LICENSED ON YEARS OF PRACTICE TO BE INCLUDED IN AMERICAN MEDICAL DIRECTORY

The Board took action authorizing the inclusion in the next edition of the American Medical Directory of only the names of graduates of medical schools with the "M.D." degree or its equivalent and physicians who have been licensed on years of practice.

MATTERS REFERRED BY HOUSE OF DELEGATES

Consideration was given to all matters referred to the Board by the House of Delegates at the Cleveland session.

FINANCES

The financial affairs of the Association were carefully reviewed, as is done at each meeting of the Executive Committee and of the Board of Trustees.

ADDRESSES BY THE PRESIDENT-ELECT

Dr. Fred W. Rankin, President-Elect of the American Medical Association, has been scheduled to deliver the following addresses:

October 1—Kentucky State Medical Association, Louisville:
The Medical Profession and Military Preparedness.

October 6—Annual fall clinical conference of the Kansas City Southwest Clinical Society, Kansas City, Mo.:
1. Indications for and Choice of Operation in Peptic Ulcer.
2. Modern Management of Carcinoma of the Rectum.
3. Diverticulitis of the Colon.

October 8—Tarrant County Medical Society, Fort Worth, Texas:
1. Diverticulitis of the Colon.
2. Modern Management of Lesions of the Lower Gastrointestinal Tract.
3. Present Day Management of Peptic Ulcer.

October 13—Columbia Medical Society, Columbia, S. C.:
Modern Management of Peptic Ulcer.

October 27—Oklahoma City Clinical Society, Oklahoma City:
1. Diverticulitis of the Colon.
2. Modern Management of Lesions of the Lower Gastrointestinal Tract.

EXHIBITS FROM HEADQUARTERS

October 1.—National Federation of Church Women, Columbus, Ohio:
"Health Education in the Doctor's Office."

October 2-4.—Mississippi Valley Tuberculosis Association, Columbus, Ohio (annual meeting):
"Health Education in the Doctor's Office."

October 6-10.—Ohio Welfare Conference, Akron, Ohio.
"Health Education in the Doctor's Office."

October 6-8.—Medical Society of Virginia, Virginia Beach (annual meeting):
"Industrial Health."

October 6-9.—Medical Society of the State of Pennsylvania, Pittsburgh (annual meeting):
Three plaster plaques: "Hippocrates, Osler and Aesculapius."

October 14-17.—American Public Health Association, Atlantic City, N. J. (annual meeting):
"Nutritionally Improved Flour."

October 19-24.—American Academy of Ophthalmology and Otolaryngology, Chicago (annual meeting):
"Physical Therapy."

October 27-31.—American Dental Association, Houston, Texas (annual meeting):
"Nutritionally Improved Flour."

October 1-30.—Tower of Health, Jackson Clinic, Madison, Wis.:
"Heroes of Medicine."
"Heart Disease."

MEDICAL ECONOMIC ABSTRACTS

STATE MEDICINE IN NEW ZEALAND

The conflict which has gone on for several years in New Zealand between the politicians and physicians as to the organization of medical service has not yet reached any satisfactory settlement. In a pamphlet entitled "The Medical Profession and Social Security Medical Services" Dr. J. P. S. Jamieson of New Zealand describes the developments up to the present time. In 1935 and 1936 a committee of the New Zealand branch of the British Medical Association recognized the imminence of legislation and made a careful investigation of health insurance throughout the world. The election held in 1935 resulted in a victory for the labor party, which was pledged to national health insurance. All the other parties also had planks in their platforms favoring health insurance.

The medical association in February 1936 offered its cooperation to the government "in formulating such changes in the health system of the country as would be suitable for our conditions." The government set up an investigating committee to study the same subject, but the committee consisted only of members of parliament of the government party and "did not include a single individual having the knowledge or experience suited for a task involving technical, scientific, professional and actuarial questions, and judicial impartiality." It was plain from the beginning that the report of the committee had been decided on in advance. The same was true of another parliamentary committee appointed in April 1938. Then, two evenings before the proposed legislation was introduced, the association was invited to a conference, at which the government presented a bill which had already been introduced into parliament and was passed immediately. This bill merely allocated the per capita sum to be distributed according to any plan for universal medical service. The government announced that it "would not consider any proposal which interposed a payment between the patient and his doctor." The physicians refused to serve under any such plan, and it has never gone into operation.

The government then proposed a similar system confined to maternity service. The medical association offered to operate this as a cash benefit to be paid to the patient. This the government refused to accept. Finally arrangements were made to "allow payment of the doctor at specified rates on certification of the services rendered."

The important differences between the original maternity contract and the new arrangement were elimination of the contract itself and the regulations, and preservation of recognition of special services, experience and higher qualifications.

Maternity is a specific thing, self limited as to sex, period of life and duration. The responsibilities of the practitioner in regard to it, though wide and varied, are finite. It lends itself to neither simulation nor self delusion beyond a certain time. In those respects it is altogether different from the rest of general practice. It was therefore possible to come to arrangement regarding it while it is quite impossible for the profession to accept, for any predetermined sum under predetermined conditions, the vast, unlimited, indeterminate sickness risk involved in general practitioner service.

In July 1939 the hospitals of New Zealand were almost completely socialized. This meant the abolition of "honorary staffs" and substitution of salaried physicians. Hospital care was then made completely free. This plan is now in operation but is developing many defects.

It was planned that the introduction of the program would be suspended during the war, but in February 1940 the medical association was "notified of the intention of the government to proceed with the matter nothwithstanding the immersion of the country in war."

In the month of December 1940, amendments were made to the Social Security Act affecting the General Practitioner Service. Finance Act (No. 4), 1940, effected repeal of certain clauses in the original act and substituted certain amending clauses. The amendments provide that a form of contract is to be drawn up in prescribed form and manner and is to be made available for any person to present to the doctor of their choice. The doctor, if he be so disposed, may sign the contract, when he will give general practitioner service to the individual at the cost of the social security fund.

The effect of these amendments is to remove from the government the duty relating to general practitioner service assumed under the original act and to place on the individual the onus of obtaining it for himself, if he can, at the expense of the social security fund. In divesting itself of this duty the government has confessed its failure.

The government was in the position of a broker who has sold to the public (and taken the money) something which he did not possess, had made no arrangements to obtain and was unable to deliver. The position now is that the broker has confessed his inability to fulfil his contract and says to his clientele "If you can get this for yourselves, I will pay."

Meanwhile the social security fund, which was to finance this contract, is already overdrawn.

The situation, therefore, still remains deadlocked at many points.

The Chicago *Tribune*, September 8, published a cable from New Zealand stating that the government has introduced a bill, which is expected to pass, providing that any doctor treating a patient after October 1 will receive a fee from the social security fund of $1 for an office and $1.25 for a home call.

WOMAN'S AUXILIARY

Idaho

Officers for the coming year for the Woman's Auxiliary to the Idaho State Medical Association will be Mrs. W. W. Beck of Blackfoot, president; Mrs. R. T. Hopkins, Orofina, president-elect; Mrs. J. W. Marshal, Twin Falls, first vice president; Mrs. W. O. Clark, Lewiston, second vice president; Mrs. B. C. Eisenberg, Pocatello, recording secretary; Mrs. H. E. Dedman, Boise, treasurer.

When Dr. Frank Lahey, President of the American Medical Association, addressed the Southwestern Idaho District Medical Society September 4, the wives of members entertained Mrs. Lahey at supper at the Owyhee Hotel in Boise. Thirty-three members from nine southern Idaho towns and from Lewiston in the north were present.

Iowa

The Woman's Auxiliary to the Upper Des Moines Medical Society met at Spirit Lake, July 10, 1941. The meeting was called to order by Mrs. C. E. Birney of Estherville. Mrs. W. R. Hornaday of Des Moines, president of the auxiliary to the Iowa State Medical Society, addressed the group on the aims and purposes of the auxiliary. The following officers were elected for the coming year: Mrs. Don F. Rodawig of Spirit Lake, president; Mrs. Paul O. Nelson of Emmetsburg, vice president; Mrs. Andrew I. Reed of Estherville, secretary and treasurer, and Mrs. Elbert E. Munger Jr. of Spencer, excommittee member from Clay County.

New Jersey

The public relations meeting of the Woman's Auxiliary to the Camden County Medical Society was held March 25, with Mrs. L. L. Glover, president, presiding. There were two hundred and twenty-five members and guests present. Mrs. O. R. Carlander, chairman of public relations, announced the program, the theme of which was "A Health Inventory." The following addresses were presented:

Are You Allergic? Dr. Harry L. Rogers.
Mental Hygiene of Childhood. Dr. Edward A. Strecker, professor of psychiatry, University of Pennsylvania School of Medicine.
Medical Supervision of the Child. Dr. Vincent Del Duca.
Heart Disease as a Public Health Problem. Dr. Ralph K. Hollinshed.

New York

At the March meeting of the Montgomery County auxiliary Miss Mildred Constantine, superintendent of the City Hospital, spoke on group hospitalization. Dr. Charles Bove, formerly of the American Hospital in Paris, addressed the Nassau auxiliary in Mineola on "Civilian Defense in Time of War." During March, Mrs. A. C. Martin introduced to the auxiliary Dr. J. F. Erdman of the New York Post-Graduate Medical School and Hospital, who spoke on the practice of medicine.

Wisconsin

Miss Gretchen Schnittger, a teacher at the orthopedic school, addressed the April meeting of the Douglas County auxiliary in Superior.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ALABAMA

Pharmacologist Dies.—Dr. Andrew Richard Bliss Jr., since 1934 head of the department of pharmacology and dean of pharmacy at Howard College, Birmingham, died in that city, August 12, aged 51. Born in New York, Dr. Bliss received his Pharm.D. at Columbia University in 1909. He received an honorary M.D. degree at Birmingham Medical College in 1914. At one time he was adjunct professor of chemistry and pharmacology at the University of Alabama School of Medicine, University, and later dean of the college of pharmacy and professor of biochemistry and pharmacology there; professor of pharmacology at the Emory University School of Medicine, Atlanta, Ga., from 1915 to 1923; chief of the division of physiology and pharmacology at the University of Tennessee College of Medicine, Memphis, from 1923 to 1933 and dean of the School of Pharmacy from 1925 to 1933; director of the Reelfoot Lake Biological Station in Tennessee from 1931 to 1936; served as a lieutenant in the Medical Corps of the U. S. Army during the World War; was a member of the Committee of Revision of the U. S. Pharmacopeia from 1930 to 1940. He was coauthor of "Laboratory Manual of Elemental Qualitative Chemical Analysis," "Physics and Chemistry for Nurses" and "Essentials of Physiology and Pharmacodynamics." At one time Dr. Bliss was a member of the Georgia Medical Society.

CALIFORNIA

Fatal Human Case of Plague.—A fatal case of human plague was reported in Siskiyou County, August 11, with onset on August 6 or 7 and death on August 9, according to *Public Health Reports*. The diagnosis was confirmed by animal inoculation and the isolation of pure cultures. The case occurred about 50 miles from the locality in which a fatal case was reported in the same county in June. It represents a new focus of the infection in California and indicates widespread rodent plague in the county, it was said.

Society News.—The Los Angeles Surgical Society devoted its meeting, September 12, to a panel discussion on surgery of the biliary tract. Dr. E. Eric Larson was the moderator, and the speakers were Drs. Larson, Harry K. Bonn, Verne C. Hunt and Isaac Y. Olch.——The Alameda County Medical Association was addressed, September 15, in Oakland by Drs. Paul R. Shumaker and Cyril J. Attwood, Oakland, on "Roentgenologic Examinations in Acute Abdominal Condltions"; Elisabeth Schulze Heald, Berkeley, "Intravenous Urography"; Lawrence M. Knox, Berkeley, "Radiologic Demonstration of Degenerative Bone Changes"; Roscoe G. Van Nuys, Berkeley, "Irradiation in Nonmalignant Diseases," and Alfred L. C. Siefert and Joseph D. Coate, Oakland, "New Methods in Roentgen Diagnosis."——The Hollywood Academy of Medicine was addressed, September 11, by Sherwin F. Wood, Ph.D., on "Chagas' Disease: A Pan American Clinical Entity."——Dr. Alfred M. McCausland, Los Angeles, discussed "Indications for and Management of Forceps in Delivery" before the San Diego County Medical Society, September 9.

ILLINOIS

Changes in Health Officers.—Dr. Charles N. Stephens, formerly of Stronghurst, has been appointed health officer for Industry and vicinity.——Dr. Paul G. Buss, formerly of Golden, has been made superintendent of the state health district with headquarters in Macomb.

Public Health Survey.—Carl E. Buck, D.P.H., field director of the American Public Health Association, is in Illinois directing a survey of the state's public health needs. The study, which will last from six to eight months, is jointly financed by the public health association and the state department of public health with the approval of the U. S. Public Health Service. On completion of the work, recommendations will be made where necessary to improve the structure of the state department of health in providing fuller protective services to the residents of Illinois.

District Meeting at Aurora.—The postgraduate conferences of the Illinois State Medical Society will open in Aurora, October 8, for the First Councilor District with Dr. Albert G. Martin, Aurora, president of the Kane County Medical Society, presiding. Speakers will be the following Chicago physicians:

Dr. James H. Mitchell, Common Skin Diseases.
Dr. Loyal Davis, Surgery of Intracranial Tumors.
Dr. Harry A. Oberhelman, Gallbladder Surgery.
Dr. Robert S. Berghoff, Arteriosclerotic Heart Disease.

In the evening Dr. Charles G. Hutter, colonel, M. C., U. S. Army, and liaison officer, War Department and the American Medical Association, Chicago, will discuss "The Medical Department of Our Army."

Chicago

Director of Behavior Clinic.—Dr. William H. Haines, acting director of the Cook County behavior clinic since July 1, was made director, September 8. He succeeds Dr. Harry R. Hoffman, who became state alienist.

The Belfield Memorial Lecture.—Dr. Henry G. Bugbee, New York, will deliver the thirteenth annual William T. Belfield Memorial Lecture of the Chicago Urological Society at the Palmer House, October 16. His subject will be "Evolution in Urology."

Society News.—The first regular fall meeting of the Chicago Laryngological and Otological Society will be addressed, October 6, by Drs. Samuel Salinger on "Stenosis and Arrested Development of the Larynx: Report of a Case Due to Irradiation for Recurring Papilloma"; George E. Shambaugh Jr., "A New Plastic Flap for Use in the Endaural Radical Mastoidectomy" (candidate's thesis), and Carl E. Cahn-Bronner, "Presence and Action of Lysozyme in the Nasal Mucus."

Dr. Hektoen Honored.—Dr. Ludvig Hektoen, executive director of the National Advisory Cancer Council, received a citation from the State Medical Society of Wisconsin during its annual session, September 10, which was the society's centennial award for distinguished service. The presentation was made by Dr. Stephen E. Gavin, Fond du Lac, chairman of the society's council, at the annual banquet. Dr. Hektoen is a native of Westby, Wis. He studied at the University of Wisconsin but graduated at the College of Physicians and Surgeons of Chicago in 1887. Dr. Hektoen is professor emeritus of pathology of Rush Medical College and the University of Chicago. He was director of the John McCormick Institute for Infectious Diseases from 1902 to 1940.

INDIANA

Society News.—Dr. Thomas Francis Jr., Ann Arbor, Mich., will conduct a clinic at Indianapolis City Hospital, October 21, on subacute respiratory disease and in the evening will address the Indianapolis Medical Society on "Epidemic Influenza." A symposium on geriatrics will be conducted before the medical society, October 28, by Drs. Cyrus J. Clark, Rollin H. Moser, Frank W. Cregor and Philip B. Reed.

Lake County Expands Mental Hygiene Activities.—Dr. Philip L. Franklin, Indianapolis, consulting psychiatrist to the state department of public welfare, has been appointed psychiatrist on a part time basis to direct the mental hygiene program in Lake County. He will live in Gary, where a mental hygiene clinic established eighteen months ago has proved the need for the extension of facilities in this field. Dr. Franklin will divide his time between Lake County and Lafayette, Peru and Plymouth, where mental hygiene clinics have been established, spending two weeks each month on Lake County cases. The facilities for this care in Lake County will be available to persons in adjoining counties who cannot afford to secure such services elsewhere, it is reported.

Government Personnel Assigned to Indiana.—The U. S. Public Health Service has assigned the following personnel to the Indiana State Board of Health to carry on public health activities in conjunction with the board and the district health departments in areas where the national defense program has greatly increased the problem of sanitation and preventive medicine:

Dr. Hugh L. C. Wilkerson, passed assistant surgeon, has been assigned to the bureau of venereal diseases and the bureau of local health administration in Indianapolis to assist in the administration of venereal disease control activities throughout the state.

Dr. Maurice Kamp, passed assistant surgeon, and Joseph R. Clark, sanitary engineer, have been assigned to district health department number 3, New Albany, to assist with the public health program in this area.

Dr. James M. Hundley, assistant surgeon, has been assigned to district health department number 7, La Porte, to assist in the administration of this district.

KANSAS

Personal.—Dr. Fred P. Helm, secretary of the Kansas State Board of Health, Topeka, has been granted a year's leave of absence to do postgraduate work at Johns Hopkins University, Baltimore. Dr. Floyd C. Beelman, Topeka, has been appointed acting secretary.

Society News.—The Wyandotte County Medical Society was addressed in Kansas City, September 2, by Dr. Fred E. Angle on "Problem of Long Continued Low Grade Fever" and Mr. C. E. Rhein, Chicago, chief of the research department on oxygen therapy of the Linde Air Products Company, "Newer Means and Methods of Oxygen Therapy."

Undulant Fever in Kansas City.—A report on the raw milk menace and the prevalence of undulant fever in Kansas City has recently been published by Dr. Ragnar T. Westman, director of health of Kansas City. In 1940 there were 165 cases reported in the state with 82 cases in Kansas City alone. Not all of these cases in the state were attributed to raw milk, since some of them were traced directly to animals, it was said. Since the first cases of undulant fever were reported in Kansas in 1927 by Col. Charles C. Hillman of the U. S. Army Medical Corps at Fort Riley, more than 1,100 cases and forty-five deaths have been attributed to the disease, giving an average of 80 cases and three deaths a year. The report points out that the recorded incidence of the disease has steadily increased. In 1940 the city department of health tested seventy-four raw milk dairies serving Kansas City and found that seventy-two dairies had cows infected with Bang's disease. Some herds had as high as 60 per cent of the cows infected, it was stated. In discussing raw milk in the report, Dr. Westman says "We have been endeavoring to improve the milk supply for some time. We have not been entirely unsuccessful, for we have induced seventeen dairies to install pasteurizers, thereby increasing the percentage of safe pasteurized milk sold in the city from 50 per cent a year ago to almost 90 per cent today. But so far we have been unsuccessful in safeguarding the remaining 10 per cent of milk sold in the city because a handful of raw milk dairymen refused to protect the public health by either testing their herds and removing their infected cows or pasteurizing their milk. Indeed, they started law suits and initiated a restraining order against the city to stop the milk improvement program."

KENTUCKY

Society News.—Speakers at a meeting of the Licking Valley Medical Society in Cynthiana, September 11, were Drs. Allen E. Grimes, Lexington, on "Problems in Hyperthyroidism"; Edward H. Ray, Lexington, "Diagnosis of Kidney Tumors"; Robert L. Loftin, Cynthiana, "Anterior Poliomyelitis," and John W. Scott, Lexington, "Water Requirements."——At a meeting of the Northeastern Kentucky Medical Association in Ashland, September 2, the speakers were Drs. Virgil E. Simpson, Louisville, on "The Problem of the Tuberculous Indigent in Kentucky"; Albert L. Bass, Louisville, "Paranasal Sinus Disease," and Francis A. Scott, Huntington, W. Va., "Backache."——Speakers at a meeting of the Four County Medical Society (Trigg, Lyon, Caldwell and Crittenden) in Eddyville, August 26, were Drs. Lillian H. South and Misch Casper, Louisville, on dysentery and on everyday surgery, respectively.

LOUISIANA

Director of Maternal Health.—Dr. William F. Guerriero, instructor in obstetrics and gynecology, Louisiana State University School of Medicine, New Orleans, has been appointed full time director of maternal and child health of the city department of health, newspapers recently reported. Dr. Guerriero is a graduate of Tulane University of Louisiana School of Medicine, New Orleans, class of 1934.

Society News.—Dr. Julius Lane Wilson, New Orleans, has been chosen president of the Tuberculosis and Public Health Association of Louisiana to fill the unexpired term of Dr. William H. Perkins, who resigned when he was named dean of Jefferson Medical College, Philadelphia.——Dr. Lucien A. LeDoux was elected president of the New Orleans Gynecological and Obstetrical Society recently.

Personal.—Dr. John Adriani, instructor in anesthesia, New York University College of Medicine, New York, resigned to become director of anesthesia at the Charity Hospital in New Orleans.——Dr. Wallace S. Sako, Minneapolis, has been appointed instructor in the department of pediatrics at the Louisiana State University School of Medicine, New Orleans, and Dr. John L. Keeley has resigned as assistant professor in the department of surgery to enter private practice in Chicago.

MARYLAND

Personal.—Samuel R. M. Reynolds, Ph.D., associate professor of physiology, Long Island College of Medicine, Brooklyn, has been appointed research associate of the Carnegie Institution of Washington, in the department of embryology, Baltimore, effective September 1.

MICHIGAN

Hospital News.—New x-ray equipment costing $7,000 has been announced for the James W. Sheldon Memorial Hospital, Albion, through cooperation of the W. K. Kellogg Foundation and the hospital's board of trustees.

Continuation Courses.—*Detroit Medical News* for September 15 has been designated the third annual bulletin of the Continuation School for Wayne County and contains a complete catalogue of the courses planned under this postgraduate activity of the Wayne County Medical Society, Wayne University College of Medicine, the hospitals of Wayne County and the Detroit Department of Health.

Society News.—Dr. H. Ivan Sippy, Chicago, discussed gastrointestinal disorders before the Muskegon County Medical Society, September 19, in Muskegon.——Dr. Walter Schiller, Chicago, discussed "New Aspects in Relation to Pathology of Ovarian Tumors" before the Calhoun County Medical Society, Battle Creek, September 9.——The Detroit Physiological Society was addressed, October 1, by Florence B. Seibert, Ph.D., Philadelphia, on "Tuberculosis as the Biochemist Sees It."

Personal.—Dr. Henry Field Jr., associate professor of internal medicine, University of Michigan Medical School, Ann Arbor, has been promoted to the rank of professor.——Dr. Abraham Leenhouts, Holland, was honored by professional and other friends, August 4, to observe his completion of fifty years in the practice of medicine and his seventy-fifth birthday.——Dr. Oscar S. Armstrong, Detroit, celebrated his ninetieth birthday, August 30. He is the oldest living past president of the Wayne County Medical Society, having served in 1892-1893. He was secretary from 1889 to 1891 and vice president in 1891-1892.——Dr. James A. Elliott, Battle Creek, has been appointed medical director of the Michigan Soldiers' Home Hospital, Grand Rapids, filling a position that has been vacant for several months.

MINNESOTA

Alumni Clinical Program.—The Alumni Association of the University of Minnesota will present its annual clinical program at the University Hospitals, Minneapolis, Friday, October 31, the day before the homecoming game between Minnesota and Northwestern University. The 1921 class of the medical school will celebrate its twentieth anniversary at this time. The committee arranging the clinical program is composed of Drs. Horace G. Scott, chairman, Harold F. Buchstein and Lucius Haynes Fowler, all of Minneapolis, and John Richards Aurelius, St. Paul.

NEBRASKA

Director of Venereal Disease Control Appointed.—Dr. James P. Sharon, at one time associated with the Iowa State Department of Health in Des Moines, has been appointed director of venereal disease control in the state health department, Lincoln. He has recently been at Fort Leonard Wood, Mo. He takes the place of Dr. Reginald A. Frary, who is on leave of absence for postgraduate study at Johns Hopkins University, Baltimore.

NEW JERSEY

Joint Meeting of County Societies.—The Bergen and Passaic county medical societies held a joint meeting in Paterson, September 11, with the following speakers: Col. Charles M. Walson, surgeon, Second Corps Area, U. S. Army, Governors Island, N. Y., on "What the Army Expects of Civilian Doctors in the National Defense Program"; Charles H. Schlichter, Elizabeth, chairman, committee on medical preparedness, Medical Society of New Jersey, "Medical Preparedness—The Physician's Duty in National Defense," and Norman M. Scott, Trenton; secretary of the state society committee, "An Analysis of the Work Done by Physicians of the Draft Boards."

NEW YORK

Personal.—Dr. Joseph Roby, deputy health officer of Rochester since 1904, retired, August 30, having reached the compulsory age limit of 70.——Dr. Wendell R. Ames, epidemiologist on the staff of the state department of health, Albany, has resigned to become health officer of Cattaraugus County.

Society News.—The New York State Association of Public Health Laboratories will hold its midyear meeting at the state laboratory in Albany, November 7.——Dr. John J. Phelan Jr., Albany, coroner's physician of Albany County, delivered his official address as vice president of the Medical Society of the County of Albany, September 24, entitled "Accident or Suicide?" ——Dr. Albert M. Biglan of the staff of the Central Islip State Hospital, Central Islip, addressed the quarterly meeting of the Suffolk County Medical Society at the hospital, July 30, on the treatment of dementia paralytica.—— Dr. Clarence O. Cheney, White Plains, addressed the Medical Society of the County of Westchester at White Plains, September 16, on "The Psychiatric Aspects of Pregnancy and Childbirth."

New York City

Courses on Venereal Disease.—Dr. Louis Chargin, consultant to the bureau of social hygiene of the New York City Department of Health, is directing a clinical course for physicians on "Diagnosis and Management of Syphilis." Sessions are held Wednesday mornings. A similar course on gonorrhea will be held Wednesday afternoons under the direction of Dr. Jacob Birnbaum.

Society News.—The Medical Society of the County of Queens met with the Queensboro Tuberculosis and Health Association, September 23; the speakers were Drs. Edgar Mayer on "Recent Aspects in the Evaluation and Treatment of Pulmonary Tuberculosis" and Louis R. Davidson, "Surgical Therapy in Pulmonary Tuberculosis and Its Evaluation." Friday afternoon lectures sponsored by the Queens County society include addresses by Drs. George A. Merrill, Brooklyn, September 19, on "Allergy"; John D. Lyttle, October 3, "Indications for Urological Investigation in Children," and Frederick H. Wilke, October 17, "Anemias of Childhood."

British Psychiatrist to Give Salmon Lectures.—Dr. Robert D. Gillespie of London, chief psychiatrist of the British Royal Air Force, will give the Salmon Memorial Lectures at the New York Academy of Medicine, November 17, 18 and 19, on "Psychoneuroses from the Standpoint of War Experience." Dr. Gillespie has been granted special leave from England to give the Salmon Lectures and will later speak in Chicago, San Francisco and Toronto, Ont. He is the author of "Disorders in Sleep" and "Textbook of Psychiatry," the latter in collaboration with Dr. David K. Henderson, Edinburgh, Scotland, a former Salmon lecturer. Before entering his wartime duties he was lecturer in psychologic medicine at Guy's Hospital Medical School in London and lecturer in psychopathology at the University of Aberdeen.

Headquarters for Blood Donations.—The New York chapter of the American Red Cross opened a new headquarters at 139 East Thirty-Sixth Street for a drive to obtain the city's quota of 200,000 blood units needed by the U. S. Army and Navy. The new space will make it possible to carry out in one place the entire operation of taking blood from donors and preserving it. Heretofore the blood has been taken from donors at Presbyterian Hospital and shipped to Philadelphia for processing. The headquarters will also be the dispatching point for the mobile unit which collects blood donations from surrounding communities, according to the New York *Times*. The staff includes a director, two physicians, seven registered nurses and a corps of technicians and other assistants. It can take care of seventy donations a day, it was said.

Three Professors Retire at Long Island.—Three members of the faculty of Long Island College of Medicine have retired and have been made emeritus professors. They are Drs. Alfred E. Shipley, professor of preventive medicine and community health; O. Paul Humpstone, professor of clinical obstetrics and gynecology, and Simon R. Blatteis, professor of clinical medicine. Dr. Shipley, who graduated from Columbia University College of Physicians and Surgeons in 1899, has been associated with Long Island since 1924, when he was made assistant professor of preventive medicine and hygiene. Dr. Humpstone also graduated from Columbia in 1899 and had been on the faculty of Long Island College since 1931. Dr. Blatteis, a graduate of Bellevue Hospital Medical College in 1898, taught for many years at his alma mater and joined the faculty of Long Island College in 1924 as clinical professor of medicine.

NORTH CAROLINA

Annual Symposium at Duke.—"Problems of Civil and Military Emergencies" will be the general subject of the annual symposium of Duke University School of Medicine and Duke Hospital, Durham, October 16-17. Among the speakers will be:

Dr. John Scudder, New York, Advances in the Treatment of Shock.
Dr. James E. M. Thomson, Lincoln, Neb., Recent Advances in the Treatment of Fractures of the Extremities.
Dr. Harry Stack Sullivan, Washington, D. C., Traumatic Neuroses.
Dr. Lewis H. Weed, Baltimore, Medical Research in Relation to the Emergency.
Dr. George J. Heuer, New York, Fundamental Principles of the Management of Wounds, Including Burns.
Dr. John F. Fulton, New Haven, Conn., Neurological Advances in the Present War.
Dr. Philip D. Wilson, New York, Experiences in the Treatment of Wounds in the Present War.
Dr. Frank D. Dickson, Kansas City, Mo., Local Use of the Sulfonamides in Wounds and Compound Fractures.
Dr. Wilder G. Penfield, Montreal, Canada, Neurosurgery During Recent Months in the London Area.
Dr. Thomas T. Mackie, New York, Problems in Nutrition During Periods of Crisis and Food Shortage.
Dr. Alvan L. Barach, New York, Clinical Use of Oxygen.
Dr. George E. Bennett, Baltimore, Recent Advances in Traumatic Surgery and Our Preparation for Their Use in War Time.
Capt. Charles S. Stephenson, M. C., U. S. Navy, Washington, Public Health Problems in Civil and Wartime Emergencies.
Dr. Russell L. Cecil, New York, Treatment of Influenza and Respiratory Epidemics.

OHIO

Rachford Lectures.—Dr. Sam Z. Levine, professor of pediatrics, Cornell University Medical College, New York, will give the annual series of Benjamin Knox Rachford Lectures at the Children's Hospital, Cincinnati, October 23-24. Dr. Levine's subject will be "Physiologic Handicaps of Prematurity: Their Pathogenesis and Clinical Applications."

University Receives Grant.—The Anheuser-Busch Company, St. Louis, has given to the University of Cincinnati College of Medicine a grant of $30,000 for the promotion of research on the part played in human nutrition by the constituents of yeast. The research is carried on under the auspices of the department of internal medicine under the direction of Dr. Tom D. Spies at Birmingham, Ala. This company had previously given the university $15,000 in grants to aid Dr. Spies in his work.

OREGON

Dr. Weinzirl to Head Public Health Department.—Dr. Adolph Weinzirl, health officer of Portland, has been appointed director of the social hygiene fund and of a new department of public health established recently at the University of Oregon Medical School, Portland, by the will of the late Dr. Ellis C. Brown (THE JOURNAL, July 19, p. 208). Under the terms of the will the director is to spend one third of his time teaching at the university and the remainder in educational work throughout the state.

PENNSYLVANIA

Acting Secretary of Health Appointed.—Dr. Alexander H. Stewart, deputy secretary of health of the commonwealth of Pennsylvania, Harrisburg, has been appointed acting secretary to succeed the late Dr. John J. Shaw. Dr. Stewart, formerly of Indiana, was appointed deputy secretary in 1939. He has served as president and secretary of the Indiana County Medical Society and trustee and councilor of the Medical Society of the State of Pennsylvania.

Society News.—Drs. William W. Richardson and John A. McKay, Mercer, addressed the Mercer County Medical Society, Mercer, September 10, on shock therapy.—— Drs. John S. Packard and William Devitt, Allenwood, addressed the Centre County Medical Society, Bellefonte, September 11, on tuberculosis.——Dr. Chevalier L. Jackson, Philadelphia, addressed the Beaver County Medical Society at the Beaver County Home, September 11, on "Bronchoscopy in Diagnosis and Treatment."

Philadelphia

Program of the College of Physicians.—At the first fall session of the College of Physicians of Philadelphia, October 1, John J. Bittner, Ph.D., assistant director of the Jackson Memorial Laboratory, Bar Harbor, Maine, delivered the Alvarenga Prize Lecture. Announcement that Dr. Bittner had received the prize was made on July 14. His subject was "The Influence of Foster Nursing on Experimental Breast Cancer." Coming speakers will be:

Dr. John B. Youmans, Nashville, Tenn., Observation on Nutrition in France, November 5.
Dr. Walter L. Palmer, Chicago, Role of Acid Gastric Juice in Gastric and Duodenal Ulceration, December 3.
Dr. John H. Musser, New Orleans, The Heart That Is Aging, Jan. 7, 1942.

Pittsburgh

Society News.—Speakers who addressed the Allegheny County Medical Society, September 16, were Drs. Ralph N. Dougherty, McKeesport, on "First Aid and Office Treatment of Fractures"; Robert L. Botkin, Duquesne, "First Aid Treatment of Burns and Further Treatment of Burns Not Requiring Hospital Treatment"; John J. McAleese, "Emergency Treatment of Injuries to the Hand and the Prevention of Disability and Deformity," and Samuel M. Dupertuis, "Correction of Deformities Following Burns and Trauma."

TEXAS

Society News.—Dr. Francis C. Goodwin, El Paso, recently addressed the Big Bend Counties Medical Society in Alpine on "Fractures and Curvatures of the Spine."——A program on tuberculosis was presented at a meeting of the Dallas County Medical Society, Dallas, September 11, by Drs. Elliott Mendenhall, George T. Caldwell, Henry F. Carman and Christopher B. Carter.

Fort Worth Medical and Surgical Clinics.—The Tarrant County Medical and Surgical Clinics will be held at the Hotel Texas, Fort Worth, October 8. The guest speakers will be Drs. Fred W. Rankin, Lexington, Ky., President-Elect of the American Medical Association; Charles W. Mayo, associate professor of surgery, University of Minnesota Graduate School, Minneapolis-Rochester, and Tom Douglas Spies, associate professor of medicine, University of Cincinnati College of Medicine, Cincinnati, and Birmingham, Ala. Col. William Lee Hart, surgeon of the Eighth Corps Area, Fort Sam Houston, discussed the medical defense program at a luncheon.

VIRGINIA

New Psychiatric Service.—A new department of psychiatry has been opened at the Medical College of Virginia Hospital, Richmond, with a capacity of thirty-eight beds. The service has facilities for hydrotherapy, a laboratory, conference room, rooms for occupational therapy. A new type of safety window screen is a special feature of the equipment. The staff will include, in addition to the professor and assistant professor of neuropsychiatry in the college, a resident, a rotating intern, graduate nurses and a social worker.

WASHINGTON

New Health Officers.—Dr. John A. Kahl, Walla Walla, has been appointed health officer of the Walla Walla county and city health department. Other new appointments are Drs. Paul L. West, Seattle, in Chelan County; Dale A. Garrison, formerly of Oklahoma City, in Jefferson County, succeeding Lawrence E. Foster, Port Townsend, and Peter D. Brink, Pomeroy, health officer of Garfield County.

GENERAL

Bequests and Donations.—The following bequests and donations have recently been announced:

Tarrytown Hospital, Tarrytown, N. Y., $25,000 as a bequest from the late Dr. Philip G. Cole.

Presbyterian Hospital, Chicago, $10,000 by the will of the late Mrs. Mary Wells.

Englewood Hospital, Englewood, N. J., $20,000 by the will of Irving Wayland Bonbright.

Lebanon Hospital, New York, $10,000 by the will of Mrs. Adele Calm Lee.

Association of Medical Colleges.—The fifty-second annual meeting of the Association of American Medical Colleges will be held in Richmond, Va., October 27-29. The speakers will include:

Col. George F. Lull, M. C., U. S. Army, The Place of the Medical Colleges in the National Defense Program.

Dr. Alvan L. Barach, New York, Physiological Problems Involved in Aviation Medicine.

Dr. Winfred Overholser, Washington, D. C., Newer Phases of Psychiatry in Relation to Army Problems.

Dr. Frank L. Apperly, Richmond, Teaching of Pathology: Criticisms and Suggestions.

Dr. Theodore Lyle Hazlett, Pittsburgh, Instruction in Industrial Medicine for Medical Students.

Dr. Fred J. Wampler, Richmond, Teaching of Industrial Health for Medical Students.

Physical Therapy Society Election.—Dr. Fred B. Moor, Los Angeles, was named president-elect of the American Congress of Physical Therapy at the annual meeting in Washington, D. C., September 1-5, and Dr. Abraham R. Hollender, Miami Beach, Fla., was inducted into the presidency. Vice presidents elected were Drs. Kristian G. Hansson, New York; Miland E. Knapp, Minneapolis; Walter S. McClellan, Saratoga Springs, N. Y.; Herbert W. Kendell, Dayton, Ohio, and Kenneth Phillips, Miami, Fla. Gold keys in recognition of distinguished services to the science of physical therapy were awarded to President Roosevelt; Mr. Bernard M. Baruch, New York; Dr. William Bierman, New York, and Dr. William S. C. Copeman of London. The 1942 meeting will be held in Pittsburgh.

The Van Meter Prize for Essay on Goiter.—The American Association for the Study of Goiter again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The essays may cover either clinical or research investigations, should not exceed three thousand words, must be presented in English and a typewritten copy must be sent to the secretary, Dr. Thomas C. Davison, 478 Peachtree Street, Atlanta, Ga., not later than April 1, 1942. The award will be made at the annual meeting of the association, June 1-3, 1942. The 1941 prize was awarded to Dr. Asher S. Chapman, Rochester, Minn., in recognition of his essay entitled "The Relationship of the Thyroid and Pituitary Glands to Iodine Metabolism and Extrathyroid Iodine Metabolism."

American Dietetic Association.—The twenty-fourth annual meeting of the American Dietetic Association will be held at the Hotel Jefferson, St. Louis, October 20-23. The speakers will include:

Dr. Russell M. Wilder, Rochester, Minn., Nutrition and National Defense.

Dr. Seale Harris Sr., Birmingham, Ala., Recent Investigations in Pellagra.

Dr. Leon Schiff, Cincinnati, Use of Meulengracht Diet in the Treatment of Peptic Ulcer.

Dr. Harry L. Alexander, St. Louis, Allergy.

Elizabeth Neige Todhunter, Ph.D., University, Ala., Measurement of Nutritional Status.

Dr. Robert Elman, St. Louis, Importance of Proteins in Surgical Healing.

Dr. John B. Youmans, Nashville, Tenn., Observations of Health Conditions in Relation to the Food Supply and State of Nutrition of Groups in France and Spain.

Proportion of Older Persons Increases.—A study made by statisticians of the Metropolitan Life Insurance Company shows that in thirty-seven large cities the number of persons 65 years old or over increased 47 per cent in the decade between 1930 and 1940; the increase in the general population for the same period was 35 per cent. Cities varied widely in the proportion of older persons in their populations. In Detroit and in Houston, Texas, only one in every twenty-four inhabitants in 1940 was 65 or over, while in Portland, Ore., the ratio was one in ten, the highest percentage of any of the large cities. Six of the eight large urban centers with the highest percentage of inhabitants at the older ages are on the Pacific Coast: San Francisco, Oakland, Los Angeles, Denver, Seattle and Portland. Three of four cities with less than 5 per cent of their populations at ages 65 and over are in the South: Houston, Birmingham and Atlanta.

Infant Mortality in 1940.—The U. S. Bureau of the Census has reported that there were 109,139 infant deaths in 1940, according to provisional tabulations. Although this was a higher number of deaths than the number for 1939, the infant death rate of 46.4 per thousand live births was about 3 per cent lower than that of the previous year, the report says, and the lowest ever recorded in the history of the birth registration area. States with the highest rates in 1940 were New Mexico with 96.9, Arizona 84.6, South Carolina 69.3, Texas 67.6 and Louisiana 63. New Mexico and Arizona showed the most notable declines: from 109 to 96.9 in New Mexico and from 94.3 to 84.6 in Arizona. The lowest rates were reported for Minnesota with 32.5, Oregon 32.6, Connecticut 33.4, Illinois 34.6 and New Jersey 34.9. San Antonio, Texas, had the highest rate among cities of more than 100,000 population with 100.4; the lowest occurred in Youngstown, Ohio, with 26.

Clinical and Climatological Association.—The fifty-eighth annual meeting of the American Clinical and Climatological Association will be held at Skytop, Pa., October 16-18. The following speakers are on the program among others:

Dr. Charles Sidney Burwell, Boston, Relation of Some Physical Signs to Alterations in the Circulation Produced by Congenital Heart Disease.

Drs. Arthur Carlton Ernstene and Robert W. Schneider, Cleveland, Angina Pectoris in Young Individuals with Aortic Insufficiency.

Drs. David T. Smith and Elijah E. Menefee Jr., Durham, N. C., Epidemic Influenza in North Carolina (1941).

Drs. Henry Stuart K. Willis and Theodore N. Rafferty, and Edna M. Jones, Northville, Mich., Primary Tuberculosis Complicated by Bronchial Tuberculosis with Atelectasis.

Drs. William S. McCann and Herbert R. Brown Jr., Rochester, N. Y., Use of Concentrated Plasma Protein Solutions in Congestive Heart Failure.

Drs. L. Whittington Gorham, Eldridge H. Campbell Jr., William P. Howard, Joseph L. Donhauser, Albany, N. Y., and Nelson H. Rust, Scotia, N. Y., Albright's Syndrome: A Group of Cases Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and a Gonadal Dysfunction.

Dr. Francis M. Rackemann, Boston, Intrinsic Asthma.

Dr. Lay Martin, Baltimore, Studies on Regional Enteritis and Some Other Conditions Causing Prolonged Partial Obstruction of the Small Intestine.

Dr. Alfred Blalock, professor of surgery, Johns Hopkins University School of Medicine, Baltimore, will deliver the Gordon Wilson Lecture on "Peripheral Circulatory Failure."

Aero Medical Association.—The thirteenth annual meeting of the Aero Medical Association of the United States will be held at the Statler Hotel, Boston, October 31-November 2. According to the preliminary program the following will speak:

Drs. William R. Lovelace II and Jan H. Tillisch, Rochester, Minn., The Physical Maintenance of Transport Pilots.

Ross A. McFarland, Ph.D., Boston, Effects of Anoxia on Certain Visual Functions.

Leon D. Carson, Surg., Lieut. Comdr., M. C., U. S. Navy, Indoctrination of Flying Personnel in the Use of Oxygen Equipment.

Drs. Lovelace and John M. Hargreaves, Major, M. C., U. S. Army, Transportation of Patients by Airplane: Indications and Contraindications.

Comdr. Eric Liljencrantz, M. C., U. S. Navy, Problems in the Selection of Student Aviators.

Capt. Richard A. Ferritt, M. R. C., U. S. Army, Corneal Transplantation: Its Value to Aviation Medicine.

Major Major S. White, M. C., U. S. Army School of Aviation Medicine, Randolph Field, Texas, Physical Disqualification of the Older Pilot.

Capt. Paul A. Campbell, M. R. C., U. S. Army School of Aviation Medicine, Randolph Field, Recent Studies of the Effect of Flight on the Ears and Hearing.

Lieut. Charles E. Kossmann, M. R. C., U. S. Army, Randolph Field, Limitations of the Electrocardiogram in the Physical Examination for Flying.

Lieut. Irving Ershler, M. R. C., U. S. Army, Randolph Field, Circulatory Responses to Anoxia in Man.

Major Otis O. Benson Jr., M. C., U. S. Army, Aeromedical Research Laboratory, Dayton, Ohio, subject not announced.

Dr. Walter A. Ostendorf, assistant chief, medical division, Civil Aeronautics Administration, Washington, D. C., Pilot Physical Examinations: Observations in the Field Here and Abroad.

Lieut. Col. David N. W. Grant, chief, medical divison, Office of the Chief of the Air Corps, U. S. Army, Washington, D. C., subject not announced.

Comdr. John C. Adams, M. C., U. S. Navy, chief flight surgeon, Bureau of Medicine and Surgery, Navy Department, Washington, subject not announced.

Drs. William R. Stovall and Albert J. Herbolsheimer, chief and assistant chief, medical section, Civil Aeronautics Administration, Washington, D. C., will conduct a forum on civil aeronautics. The program will conclude with the installation as president of Comdr. John R. Poppen, M. C., U. S. Navy, and the presentation of the past president's pin to Dr. Herbert F. Fenwick, Chicago.

Mental Hygiene Report.—According to the thirty-first annual report of the National Committee for Mental Hygiene, recently published, a nationwide survey by the committee showed there was an estimated deficit of one hundred and fifty thousand beds for the treatment of the mentally ill, with long waiting lists of patients, many of whom languish in jails for want of hospital facilities. It is not the doctors who are to blame, the report explains, so much as legislative inaction and public indifference. Recognizing that a major factor in the state hospital burden is the vast accumulation of patients afflicted with dementia precox, the committee is administering a series of researches, subsidized by the Supreme Council 33°, Northern Masonic Jurisdiction, in which one hundred investigators, working in twelve universities and sixteen hospitals, are studying various aspects of the problem. A recent survey of child guidance and mental health clinics showed an increase and development in these services with seven hundred and fifty clinics in operation in four hundred and fifty cities, towns and villages in thirty-five states.

A study of personnel practices in twenty-two teacher training colleges in five Eastern states resulted in the establishment of three experimental projects in teachers' colleges in San Diego, Calif., Trenton, N. J., and New Haven, Conn., to determine favorable or adverse personality factors that should be considered in encouraging or excluding students from a teaching career. An increase is noted in psychiatric instruction in leading medical schools in the country, from sixty-four and eight-tenths hours in sixty-five medical schools in 1932 to ninety and three-tenths hours in sixty-seven schools in 1940. There was an increase in psychiatric teaching in the preclinical years from sixteen and one-tenth hours in twenty-nine schools in 1932 to twenty-six and four-tenths hours in fifty-nine schools in 1940.

The report recommends the rigid exclusion of the mentally and nervously unfit from the armed forces and more adequate medical examinations of selectees. Many cases of mental and nervous disorders have passed through the local draft boards because the average medical examiner is not psychiatrically trained to detect them, while at the induction centers where psychiatrists are available their number is too small and the time allowed to them is too limited for thorough examinations. Efforts to remedy this situation include the regional conferences and seminars which the Selective Service Administration is conducting throughout the country for the instruction of examiners and the development of more effective methods of psychiatric examination. The report discusses the problem of the management of draftees who are rejected for mental or nervous disorders and need help, whose stability may be further shaken as a consequence of rejection. To meet this problem, it suggests that the acceptance of men for military service be regarded as a matter of vocational fitness and the process of examination as one of selection.

PHILIPPINE ISLANDS

New Board of Medical Examiners.—The secretary of the department of health and public welfare has appointed a new board of medical examiners, according to the *Journal* of the Philippine Medical Association. Dr. Jose V. de los Santos, Manila, is chairman and the members are Drs. Ramon F. Campos, Iloilo, and Aurelio R. Santos, Manila.

LATIN AMERICA

Society News.—Announcement is made of the formation of the Society of Gastro-Enterology and Nutrition of São Paulo, Brazil, with the following officers: Drs. Levy de Azevedo Sodre, president; Vasco Ferraz Costa, general secretary; Francisco Xavier Pinto Lima, assistant secretary; João Alves Meira, treasurer, and Edison de Oliveira, librarian.

Personal.—Dr. Trino Castro, surgeon of the orthopedic clinic of Santa Elisa and director of the Venezuelan Foundation for Infantile Paralysis, Caracas, Venezuela, visited the United States to attend the annual meeting of the American Congress of Physical Therapy in Washington, September 1-5. Dr. Castro is also chief of the traumatologic and orthopedic service of the Naval and Military Hospital of Caracas.

FOREIGN

Society News.—The Permanent Commission of the League of Red Cross Societies recently decided to postpone indefinitely the seventeenth International Red Cross Conference, which was to have been held at Stockholm, Sweden, in 1942.

Plan Tuberculosis Wing for Jerusalem Hospital.—Hadassah, the Women's Zionist Organization of America, has made a grant of $35,000 to the Rothschild-Hadassah-University Hospital in Jerusalem toward a special fund for a new tuberculosis wing for the hospital. The organization has already sent $20,000 to Palestine during the past year for support of the sixty bed Safed Tuberculosis Hospital and its subsidy to the Anti-Tuberculosis League for treatment and preventive work among children. Reports from Palestine indicate that tuberculosis has greatly increased in Palestine because of inadequate facilities for medical care coupled with crowded living conditions, a breakdown in nutrition standards and the heavy influx of refugees into Palestine.

British Vital Statistics for 1940.—Vital statistics for 1940 in England, which recently became available, show a death rate of 14.3 per thousand among the civil population, the highest since the World War, according to a report issued by the Metropolitan Life Insurance Company. Infant mortality, 55 per thousand live births, was lower than that of any year prior to 1939. The birth rate was 14.6 per thousand of population. The marriage rate was said to be the highest in English history and nearly 30 per cent above the prewar rate. Data for 1941, available only for London and the large cities, show trends less favorable than in 1940, the statement said. The death rate is high because of the bombings in the early part of the year, and infant mortality is high because of the prevalence of communicable diseases, especially measles, whooping cough and diphtheria. The birth rate has declined sharply as compared with the first half of 1940. For the country as a whole, civilian air raid deaths in the first half of 1941 number approximately nineteen thousand.

Foreign Letters

LONDON

(From Our Regular Correspondent)

Aug. 2, 1941.

Food Situation Satisfactory

In the House of Commons the minister of agriculture, Mr. R. S. Hudson, stated that the food situation is much more encouraging than he dared to hope a year ago. Assuming reasonable weather, we can rely on the farmers producing a larger supply of food than in any previous year of the century. The magnificent crops to be seen in the country were due to improved and more scientific cultivation. Despite the inevitable reduction of imported food, owing to the war, it should be possible to assure our people that in the third year of war the quantity of food in terms of food values will be not only greater than in the second year but at least as great as it was in peacetime and possibly greater. In this connection it should be remembered that, as shown in previous letters to THE JOURNAL, thanks to the great attention given to nutrition by the government, there is in this second year less malnutrition than there was before the war, though there is considerable restriction of certain foods, particularly meat. Mr. Hudson qualified his forecast only to the extent that we would have to rely more on potatoes, cereals and vegetables and a slight change of emphasis from proteins of animal origin to those of vegetable origin. We are drinking annually in England and Wales 880 million gallons of milk compared with 760 before the war. The Germans are devoting most of their milk to the manufacture of butter, but we are importing butter and cheese. We cannot import feeding stuff for animals to the prewar extent, but many potential feeding stuffs are being brought into use for the first time. Foremost is the waste foodstuffs from the towns, which, when supplemented with concentrates, form a valuable feeding stuff for pigs and poultry. We are plowing up hitherto uncultivated land, including golf courses. Farmers are being asked to plow up this year another 2,000,000 acres, and if the war continues we shall gradually take the plow round England. In the last twelve months we have produced more food than ever before in this country.

The food situation may be summarized as follows: The great curtailment of imported food, on which we largely depend in peacetime, is to a large extent offset by increased home production. By rationing and subsidizing, food is brought within the means of the poorest and luxury consumption by those who could afford it is reduced. Hence the fact, claimed by the minister of food, that there is less malnutrition than in peacetime. Our supplies of animal food, particularly butter, are reduced and we have become more vegetarian. But that is no disadvantage as far as nutrition is concerned, and in the case of some persons it is an advantage.

In the House of Lords the minister of food, Lord Woolton, said that the problem of food control never could be simple and often resolved itself into a competition between the relative merits of the things that were good for us and the things that were not so good but which we wanted even more. The country had become more sensitive to the question of malnutrition than it ever was in peace. He was confronted with the difficulty not only that had our supplies been reduced but that they were constantly changing in character, sometimes rapidly, as the course of battle removed sources. If we still had the Netherlands and Denmark to trade with, there would be no concern about milk, cheese, butter or eggs. If we had the Channel islands, we should have had supplies of early potatoes and there would have been no problem of tomatoes. But for the battle of the Atlantic there would have been few difficulties about meat. Yet, in spite of the nervous strain of air raids, as a nation we were fit and well. He would venture the speculation that there were fewer people suffering from malnutrition now, at the end of the second year of the war, than in the days of peace. This was apparently due to the government policy of securing not only adequacy of supplies but adequacy of distribution according to people's needs. As a result of the organization of food distribution and of selling at a price within the reach of the ordinary housewife, many were more adequately fed than before the war. We had so husbanded our stocks of food that we stood alone among the warring nations in being able to increase rations. We could look to the future with much confidence. While this year the nutritive values of the foods in this country had suffered some decline, next year they should be as high as they had ever been in the last fifteen years. As a result of the generous provision being made by the United States, he hoped to be able to remedy lack of variety from now onward.

Clothing and Footwear Rationed

Clothing and footwear have been rationed for the same reason as food has been—so that restriction of supply will fall equally on rich and poor. Clothing, cloth, footwear and knitting wool cannot now be bought without giving up coupons, of which sixty-six are allowed to each person for a year. For the purchase of an overcoat or raincoat sixteen coupons are required; of a coat, jacket or blazer, thirteen; of trousers, eight; of a night shirt or pyjamas, eight; of a collar, tie or pair of cuffs, one; of a pair of boots, seven. Women and children are similarly restricted. Coupons will not be required by persons receiving assistance from the government to enable them to replace clothing lost by enemy action. In a broadcast outlining the scheme Mr. Lyttelton, president of the board of trade, said that people could buy what they liked with the coupons which were concerned with the various articles and had nothing to do with price. "I know," he said "that all the women will look smart, but we men may look shabby but this will be honorable."

More Children Killed on the Roads

An indirect effect of the war is that more children are killed in traffic accidents on the roads. The Royal Society for the Prevention of Accidents has just completed an analysis of wartime road accidents. It finds that children are now being killed at the rate of more than three a day and that since the spring of 1940 these deaths have increased by more than 50 per cent. From September 1939 to February 1940 359 child pedestrians were killed. From September 1940 to February 1941 the number was 558. Few children are killed after dark. As before the war, children between the ages of 3 and 8 years are the most numerous victims.

Large Decrease in Air Raid Casualties

The Ministry of Home Security has published figures for the air raid casualties in June, which show a large decrease. The killed number 399 and the injured and detained in hospitals 461. Of the killed 175 were men, 160 women and 64 children under 16. Of the injured 239 were men, 175 women and 47 children under 16. The difference from the preceding months is vast. In May 5,394 were killed, in April 6,065, in March 4,259, in February 789 and in January 1,502. The total killed in the first six months of the year was 18,408. In the previous six months 23,960 civilians were killed.

Dr. A. Brown Kelly

Dr. A. Brown Kelly, a laryngologist of international reputation, has died in retirement in his seventy-sixth year. He graduated at Glasgow University and became surgeon to the ear, nose and throat department of the Victoria Infirmary in Glasgow. He was corresponding member of the Society of Laryngology of France, the American Laryngological Society,

the Laryngological Society of Berlin and the Rhinological Society of Vienna. He edited the Transactions of the Section of Laryngology and Rhinology of the seventeenth International Medical Congress. His Semon lecture at the University of London on "Nervous Affections of the Esophagus" was a noteworthy contribution. He wrote thirteen papers on pharyngeal diseases and abnormalities, all the result of painstaking and original investigation. He was a shy and diffident man whose only recreation, apart from pathologic research, was orchestral music. He never sought honors, though many came to him.

BUENOS AIRES

(From Our Regular Correspondent)

July 5, 1941.

South American Congress of Sports Physicians

The second South American Congress of Sports Physicians was recently held in Buenos Aires. Delegates from Bolivia, Brazil, Colombia, Chile, Ecuador, Peru, Uruguay and Venezuela participated. The subjects treated were sports for women from the medical point of view, the effect of geographic altitude on sports efforts and the evaluation of cardiopulmonary effort in sports activities. Medical discussion included long distance running, therapies pertaining to sports activities and the relation of nutrition to sports. The resolutions adopted at the close included the continued study of the effect of altitudes on sports exertions, especially of the time required to condition the individual for altitude sports and of the limits of physical exertion from the point of view of individual health. Gymnastic exercises for women were regarded as highly useful. Sports activities should be selected by women in accordance with their biotype, their physical strength and their health. The legal aspects involved in accidents occurring in professional sports are to be investigated. Sports contestants should be given roentgenologic and tuberculin examinations. The next congress will meet in 1943 in Montevideo, Uruguay.

Report of the Cancer Institute in Buenos Aires

Recently the cancer institute at Buenos Aires, directed by Prof. Angel H. Roffo, published a report of its clinical activities for the years 1937-1939. The number of patients registered now exceeds 90,000. From about 1,800 in 1923 the number rose to 7,300 in 1939. Consultations increased from 6,800 to 77,900. In 1932, 34.9 per cent of the registered cancer patients were Argentinians. In 1939 their number was 42.6 per cent. The increase is attributed to reduced immigration during the last years. In 1926, 50.8 per cent were males; in 1939, 57.4 per cent were of this sex.

An increase in carcinoma of the skin has been observed in the last decade (11.08 per cent in 1930; 21.77 per cent in 1939). Carcinoma of the respiratory tract increased from 6.18 per cent to 12.72 per cent during the same period. Carcinoma of the stomach remained unchanged; that of the uterus decreased. New wards have been added, courses for physicians have been established and a department of cancerology has been organized in the faculty of medicine of the University of Buenos Aires. Affiliated cancer stations are maintained in the interior of the country.

Control of Cancer

A division for the prophylaxis of carcinoma and the dissemination of scientific information has been organized in the national department of health of Argentina. The creation of this health agency is due to the alarming increase of tumor growths reported in this country and the number of cancer patients who seek treatment in such an advanced stage of the disease that therapeutic measures are unavailing. The new cancer division is to establish in the health stations of the interior the necessary foundation for the effective work of roentgenologists and surgeons and to serve as a supply center for all materials needed in a nationwide active program. It also is charged with the functions of performing early diagnosis and of the transportation and care of cancer patients regarded as remediable.

Obstetric Clinics in Chile

The ministry of health in Chile has ordered new regulations governing private obstetric clinics and midwives. Every room of a physician and midwife in which delivery is performed will hereafter be included under the regulations. A threefold classification is made according to the number of beds. Clinics must be officially authorized and accurate records maintained. Midwives may not employ general narcotics. The medicaments which they may use are specifically designated. The regulations also determine who may be admitted. A minor may be admitted only with the consent of her husband, father or guardian. The attestation of three physicians is required, one of whom must be a specialist. He assumes responsibility for the obstetric intervention.

Brief Mention

The council of the University of Buenos Aires, at the request of the faculties of medicine, has suspended for five years the regulations permitting the registration of medical degrees obtained abroad. The only exception made is in behalf of native Argentinians who took their degree abroad. The University of La Plata recently passed a similar resolution. These measures will make it difficult for foreign physicians to establish themselves in Argentina. At present such registration is still possible at the universities of Córdoba and Rosario.

Virginio Grego, an industrialist, has given the faculty of medicine 100,000 pesos ($29,770) for the construction of an institute for circulatory investigation, an additional 50,000 pesos ($14,885) for equipment and 40,000 pesos ($11,908) annually for maintenance. At the founder's request the institute will be directed by Dr. Alberto Taquini. The university has accepted the gift and will furnish the personnel.

The Rockefeller Foundation has made a grant of $4,000 to the physiologic institute of the university of Buenos Aires for the training of young scientists.

Marriages

CLARENCE E. OWENS, Columbia, S. C., to Miss Marion E. Flager of St. Augustine, Fla., July 14.

RAYMOND SHETTEL, Mount Wolfe, Pa., to Miss Helen Louise Myers of York, July 18.

JOHN EDWARD FIELD, Sheridan, Ore., to Miss Anne Erskine of Portland, July 6.

JOHN B. BARNELL to Miss Inez Erminie D'Amanda, both of Rochester, N. Y., June 30.

HARRY LEE ARCHER to Miss Sarah Gordon Wilson, both of Charlottesville, Va., in July.

PAUL G. SHELL, Fort Lauderdale, Fla., to Miss Velna Loraine Fay of Howell, Mich., July 8.

GEORGE CATLETT ROWE to DR. MARY VIRGINIA COPELAND, both of Atlanta, Ga., in Marion, N. C., July 16.

JAMES G. JEANES, Clinton, S. C., to Miss B. Joann Sawicz of Palm Beach, Fla., June 26.

FRANK PATTON GASTON to Miss Dora Jones Dunlap, both of Rock Hill, S. C., in July.

THADDEUS B. REEVES, Greenville, S. C., to Miss Julia Gambrill Smyth of Flat Rock, July 22.

SAMUEL DUBOSE MURRAY, Pensacola, Fla., to Mrs. Virginia White Whitaker of Atlanta, Ga., July 12.

JAMES REEDER MCMILLAN, Decaturville, Tenn., to Miss Margaret Moore of New York, July 17.

JACK JOHN HLADYCZ, Perth Amboy, N. J., to Miss Virginia Ellis in Aberdeen, Md., recently.

JOHN DENT SUMMERS, Statesville, N. C., to Miss June Rogers of Burlington, Iowa, June 21.

Deaths

Joseph Rigney D'Aunoy ✠ New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1913; since 1931 professor of pathology and bacteriology and from 1937 to 1939 dean at the Louisiana State University School of Medicine; instructor of pathology and bacteriology at his alma mater from 1919 to 1924; member of the American Association of Pathologists and Bacteriologists, American Society for Experimental Pathology, Society of American Bacteriologists and the American Society of Clinical Pathologists; in 1939 was appointed to serve as a member of the board of the Guidance Center of the New Orleans Institute of Mental Hygiene; pathologist and director of laboratories, Charity Hospital; in 1933 was awarded an honorary fellowship by the Gorgas Medical Society of New Orleans; on the editorial board of the *Journal of Tropical Medicine and Hygiene;* director of laboratories of Base Hospital number 86, American Expeditionary Force, from 1918 to 1919; aged 51; died, September 17, of hypernephroma of the left kidney.

William Henry Riley, Battle Creek, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1886; member of the Michigan State Medical Society, Association for Research in Nervous and Mental Disease and the Central Neuropsychiatric Association; at one time professor of nervous and mental diseases at the University of Colorado School of Medicine, Boulder, and the American Medical Missionary College; fellow of the American College of Physicians; for many years on the staff of the Battle Creek Sanitarium; superintendent of the Boulder Colorado Sanitarium and Hospital from 1896 to 1902; aged 81; died, August 24, near Mattoax, Va.

Edward Binney Lane, Milton, Mass.; Harvard Medical School, Boston, 1885; member of the Massachusetts Medical Society, American Neurological Association and the American Psychiatric Association; past president of the Boston Society of Psychiatrists; since 1928 emeritus professor of mental diseases, and from 1903 to 1928 professor at the Tufts College Medical School, Boston; clinical instructor of mental diseases at his alma mater from 1898 to 1903; superintendent of the Boston State Hospital from 1895 to 1905; formerly medical superintendent of the Adams Nervine, now known as the Adams House; aged 81; died, September 17.

William Rosenberg ✠ Cleveland; Western Reserve University School of Medicine, Cleveland, 1919; member of the American Urological Association; fellow of the American College of Surgeons; past president of the Cleveland Urological Society; chief of the department of urology at the Mount Sinai Hospital; aged 47; died, August 20, of adenocarcinoma of the large intestine with metastases.

Juan C. Nanagas y Padua, Manila, Philippine Islands; University of the Philippines College of Medicine, Manila, 1915; in 1921 member of the House of Delegates of the American Medical Association; member and past president of the Philippine Medical Association; past president of the Manila Medical Society; professor of anatomy at his alma mater; aged 52; died, June 4.

Joseph Romeo Toupin, Montreal, Que., Canada; M.B., Laval University Medical Faculty, Montreal, in 1907 and M.D., in 1909; member of the Provincial Parliament; formerly associate professor of dermatology and syphilology at the University of Montreal Faculty of Medicine; was chief of the department of dermatosyphilography at St. Luke's Hospital; died, August 2.

Morgan John Rhees, Boston; Harvard Medical School, Boston, 1925; member of the Massachusetts Medical Society; director of the Joseph H. Pratt Diagnostic Hospital; for many years assistant director of the Massachusetts General Hospital; aged 41; died, August 25, at his summer home in Islesford, Me., of coronary occlusion.

William W. Kerns, Bloxom, Va.; University College of Medicine, Richmond, 1896; member of the Medical Society of Virginia; past president of the Accomac County Medical Society; formerly bank president; aged 70; died, August 29, in the Northampton-Accomac Memorial Hospital, Nassawaddox, of coronary occlusion.

James Weaver Conley, Quanah, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1908; member of the State Medical Association of Texas; served during the World War; aged 57; died, August 18, in a hospital at Wichita Falls of bilateral urethral calculi.

Luther Archibald Youngs, Paradis, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1908; member of the Louisiana State Medical Society; aged 63; died, June 15, in the Baptist Hospital, New Orleans, of carcinoma of the face and arteriosclerotic heart disease.

Edward Orlando Tabor ✠ Lowell, Mass.; Dartmouth Medical School, Hanover, N. H., 1901; served during the World War; school physician; on the staffs of the Lowell General Hospital and St. Joseph's Hospital; aged 64; died, August 25, of pulmonary edema.

Houston Boyd Hiatt, Oldsmar, Fla.; University of Maryland School of Medicine, Baltimore, 1907; member of the Medical Society of the State of New York; past president of the Guilford County (N. C.) Medical Society; aged 54; died, August 28, in Tarpon Springs.

William Ernest Cary ✠ Chicago; Rush Medical College, Chicago, 1921; assistant clinical professor of medicine at the University of Chicago, The School of Medicine; attending physician on the staff of the Chicago Memorial Hospital; aged 52; died, August 29.

Arthur Leighton Sherman, New York; Columbia University College of Physicians and Surgeons, New York, 1904; member of the Medical Society of the State of New York; aged 63; died, August 24, in the Lutheran Hospital of carcinoma of the prostate.

Mary E. Macallum Scott, Newton, Mass.; Woman's Medical College of the New York Infirmary for Women and Children, New York, 1891; formerly a medical missionary; aged 76; died, August 26, in Tuckahoe, N. Y., of cerebral arteriosclerosis.

Oliver Chambers ✠ Rock Springs, Wyo.; University of Nebraska College of Medicine, Omaha, 1903; fellow of the American College of Surgeons; on the staff of the Wyoming General Hospital; aged 66; died, August 8, of coronary thrombosis.

Manly Coke Smith, Simpsonville, S. C.; University of Maryland School of Medicine, Baltimore, 1913; member of the South Carolina Medical Association; served during the World War; aged 53; died, August 21, of cerebral hemorrhage.

Harriet Beecher Conant McLoud, Minneapolis; University of Minnesota College of Medicine and Surgery, Minneapolis, 1891; aged 89; died, August 22, in the Northwestern Hospital of general peritonitis and perforated appendix.

John McMurray Cassidy, Jersey City, N. J.; University and Bellevue Hospital Medical College, New York, 1912; member of the Medical Society of New Jersey; on the staff of the Greenville Hospital; aged 55; died, August 22.

Harry Bertolette Kurtz, Cleveland; Western Reserve University Medical Department, Cleveland, 1893; aged 71; for many years on the staff of St. Luke's Hospital, where he died, August 21, of hypertensive cardiovascular disease.

Walter Fischbein, Woodmere, N. Y.; Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main, Prussia, Germany, 1917; member of the Medical Society of the State of New York; aged 47; died, August 24.

J. Frank Cornell, Galveston, Ind.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1902; aged 71; died, August 27, in St. Joseph's Hospital, Kokomo, of mesenteric thrombosis.

Frank Palmerston Hough, Binghamton, N. Y.; Jefferson Medical College of Philadelphia, 1884; member of the Medical Society of the State of New York; aged 82; died, July 10, in the City Hospital of cerebral hemorrhage.

William Ogden Lord, New Bedford, Mass.; Columbia University College of Physicians and Surgeons, New York, 1903; member of the Massachusetts Medical Society; aged 60; died, August 8, of coronary thrombosis.

Gilbert Haven Ayling ✠ Kankakee, Ill.; Northwestern University Medical School, Chicago, 1909; served during the World War; on the staff of St. Mary's Hospital; aged 59; died, August 29, of coronary occlusion.

Curtis C. Hamilton, Linton, Ind.; Eclectic Medical Institute, Cincinnati, 1908; member of the Indiana State Medical Association; aged 57; died, August 30, in the University Hospital, Ann Arbor, of a brain tumor.

Ezra Newton Drier, Vancouver, B. C., Canada; McGill University Faculty of Medicine, Montreal, Que., 1899; served with the Canadian Army Medical Corps during the World War; aged 69; died, June 27.

Ellis Marshall Harvey ✠ Media, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1893; aged 72; died, August 24, in the Bryn Mawr (Pa.) Hospital of cerebral thrombosis and hypertension.

Frank Fletcher Pope, Ashby, Mass.; Dartmouth Medical School, Hanover, N. H., 1885; member of the Massachusetts Medical Society; aged 82; died, August 26, of uremia, chronic nephritis and heart disease.

Marcus Gersh Wolk, Chicago; University of Tomsk Faculty of Medicine, Tomsk, Siberia, 1912; member of the Illinois State Medical Society; aged 60; died, July 7, of embolus and cerebral hemorrhage.

Charles Emerson Soule ✠ Beardstown, Ill.; College of Physicians and Surgeons of Chicago, 1889; president of the Cass County Medical Society; secretary of the school board; aged 78; died, August 14.

Charles Robert Knapp, Forest City, Pa.; Albany (N. Y.) Medical College, 1885; formerly county coroner; school physician; on the staff of the Carbondale (Pa.) General Hospital; aged 77; died, August 9.

Louise Southgate, Covington, Ky.; Woman's Medical College of Cincinnati, 1893; Presybterian Hospital and Woman's Medical College, Cincinnati, 1893; aged 84; died, August 15, of gastric hemorrhage.

Jesse Albert Moore, Sharon, Tenn.; Vanderbilt University School of Medicine, Nashville, 1900; for many years mayor and member of the school board; aged 66; died, August 15, of coronary thrombosis.

John Finley Miller, Akron, Ohio; Starling Medical College, Columbus, 1895; member of the Ohio State Medical Association; aged 74; died, August 19, in the City Hospital of heart disease.

Philip John Lewert ✠ Scranton, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1913; on the staff of the Hahnemann Hospital; aged 51; died, August 27, of subacute endocarditis.

George Alexander Ragoff, Newark, N. J.; Chicago College of Medicine and Surgery, 1913; aged 53; died, July 31, of peripheral circulatory failure following an operation for pyloric obstruction.

Harland Everett Dice ✠ Moroni, Utah; State University of Iowa College of Homeopathic Medicine, Iowa City, 1908; formerly mayor; aged 58; died, August 27, of coronary thrombosis.

Frank Cutler Linden ✠ Chicago; College of Physicians and Surgeons of Chicago, 1889; aged 80; died, August 30, at Neosho, Wis., of injuries received in an automobile accident.

Shober Smith, Barnesville, Ohio; University of Pennsylvania School of Medicine, Philadelphia, 1910; served during the World War; aged 57; was found dead in bed, August 14.

John Lawrence Travis, Germantown, Ohio; Miami Medical College, Cincinnati, 1890; served during the World War; aged 75; died, August 15, of cerebral arteriosclerosis.

William Tignor Gill Sr., ✠ Washington, D. C.; Columbian University Medical Department, Washington, 1887; aged 75; died, August 26, of heart disease and arteriosclerosis.

Charles A. Wilson, Houston, Texas; Medical College of Ohio, Cincinnati, 1879; aged 85; died, in August of injuries received when he fell from a fourteenth story window.

John Lincoln Hertz ✠ Lititz, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1892; served during the World War; aged 77; died, August 25.

Henry Eugene Potvin, Providence, R. I.; School of Medicine and Surgery of Montreal, Que., Canada, 1905; aged 63; died, August 18, in the Charles V. Chapin Hospital.

Stephen Napoleon Bonaparte Penland, Madisonville, Tenn.; Vanderbilt University School of Medicine, Nashville, 1890; aged 87; died, August 31, of heart disease.

Alexander Lough Eddy ✠ Greensboro, Pa.; College of Physicians and Surgeons, Baltimore, 1902; aged 69; died, August 20, in a hospital at New York.

Frank P. Walker, Jacksonville, Fla.; Jefferson Medical College of Philadelphia, 1878; aged 86; died, August 12, of myocarditis and carbuncle on the back.

John T. White, Gainesville, Mo.; Barnes Medical College, St. Louis, 1899; aged 71; died, June 22, in St. John's Hospital, Springfield, of an abscess of the lungs.

Robert Bertram Klotz, Breinigsville, Pa.; Jefferson Medical College of Philadelphia, 1893; aged 68; died, August 27, in the Allentown (Pa.) Hospital.

Henry Granger Haxby, Tempe, Ariz.; University of Denver Medical Department, 1892; aged 80; died, August 22, of chronic myocarditis and nephritis.

Samuel McCallum, Niagara Falls, Ont., Canada; Queen's University Faculty of Medicine, Kingston, 1906; aged 61; died, August 23, of coronary thrombosis.

Edgar Israel Raymond, Wellington, Colo.; Gross Medical College, Denver, 1896; member of the Colorado State Medical Society; aged 73; died recently.

Walter Seymour Brown, Oakley, Kan.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1885; aged 80; died, August 5.

Oswald Patrick Goodall ✠ Bakersfield, Calif.; St. Louis University School of Medicine, 1913; aged 57; died, July 3, of a self-inflicted bullet wound.

Clarence H. Gardner, Tucson, Ariz.; University of the City of New York Medical Department, 1885; aged 76; died, August 17, in La Jolla, Calif.

William Alonzo Cooper, Bayard, Iowa; Hahnemann Medical College and Hospital, Chicago, 1902; aged 64; died, July 6, of fibromyosarcoma.

John Clark Haller, Cleveland; Cincinnati College of Medicine and Surgery, 1882; aged 84; died, August 16, in the Fairview Park Hospital.

Giuseppe Bonaccolto, New York; Regia Università degli Studi di Palermo Facoltà di Medicina e Chirurgia, Italy, 1894; aged 76; died, July 30.

Frank A. Strawbridge, Sigourney, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1886; aged 82; died, July 31.

Hubert William Hancock, Chicago; St. Louis College of Physicians and Surgeons, 1918; aged 56; died, July 7, of coronary thrombosis.

James Ward Messersmith, Forgan, Okla. (licensed in Oklahoma under the Act of 1908); aged 69; died, June 25, of heart disease.

Joseph F. Trudnowski ✠ Buffalo; University of Buffalo School of Medicine, 1916; aged 54; died, August 20, of cerebral hemorrhage.

Wiley Aven Preston, Abingdon, Va.; Medical College of Virginia, Richmond, 1941; aged 37; died, August 27, in Richmond.

George MacDonald Albee ✠ Worcester, Mass.; University of the City of New York Medical Department, 1893; fellow of the American College of Physicians; aged 70; died, August 10.

Benjamin F. Hamrick, Madison, Fla.; Georgia College of Eclectic Medicine and Surgery, Atlanta, 1913; aged 55; died, August 18.

Lorin Edgar Kerr Sr., Toledo, Ohio; Toledo Medical College, 1905; served during the World War; aged 62; died, August 15.

Edward Samuel Read, Montreal, Que., Canada; McGill University Faculty of Medicine, Montreal, 1909; aged 59; died, August 12.

Percy Weeks Barker, Vancouver, B. C., Canada; University of Toronto Faculty of Medicine, 1910; aged 59; died, July 30.

Barbara Taylor Ring ✠ Arlington, Mass.; Boston University School of Medicine, 1899; aged 67; died, August 31.

Augustus Harper Buckmaster, Bexley, Ohio; Long Island College Hospital, Brooklyn, 1883; aged 81; died, August 31.

John Benton Buell, Stevensville, Ont., Canada; Trinity Medical College, Toronto, 1901; aged 68; died, August 23.

Julius Wirth, Highland, Ill.; New Orleans School of Medicine, 1870; aged 94; died, August 15.

Bureau of Investigation

R. A. WINTERS, M.D.

Itinerant Principal of Unsponsored Postgraduate Course

The Bureau of Investigation first encountered the name of Dr. R. A. Winters in the advertising of "Diatone." The advertisement was a reprint of an article by Winters from the January 1936 issue of the *American Journal of Physical Therapy*. In this article he stated in part:

> "I have successfully used for some time, colloidal uranium (Diatone) . . . In thirty cases treated recently, three had been receiving insulin injections which were gradually withdrawn. Twenty-nine of the thirty showed a marked recovery, with a definite control of the symptoms. . . . one case that did not respond . . . showed a four plus Wassermann . . ."

In this article he also suggested "medications, colonic flushings or other therapeutic aids as indicated" and added "Short Wave Radiations through the pancreas have been known to aid in a more rapid stimulation of its tissues. Deep massage to the abdomen is a very helpful aid."

In February 1937 the Food and Drug Administration issued a Notice of Judgment against Diatone, because it was fraudulently represented as a remedy for diabetes. A month later—in March 1937—it was reported that Diatone, Inc., had gone out of business, having filed a Notice of Dissolution.

Prior to this—in November 1936—the *Bulletin of the Erie County Medical Society*, Buffalo, published a statement under the title "Young Doc Winters Arrives, Lectures and Departs." This note indicated that he lectured in Buffalo November 9 and 10 on "Needle Surgery." It referred also to his apparent connection with the Farnsworth Laboratories and mentioned that concern's product "Alphacatalyst." The Bureau published a report on this treatment in THE JOURNAL for May 6, 1933, which concluded in part as follows:

> "In spite of the fact that the Alphacatalyst (Oxycatalyst) has been on the market six years, there is still no scientific evidence to indicate that it has any value."

A previous article appeared on this preparation in THE JOURNAL for May 19, 1928.

The Buffalo item also referred to the fact that Winters was reported to be dean of the American College of Physical Therapy, which organization was exposed in THE JOURNAL for Sept. 23, 1933 at a time which was apparently prior to Winters' connection with it. The conclusion of this article read in part as follows: "Of course, the 'college' has not been approved by the Council on Medical Education and Hospitals of the American Medical Association. . . . It is to be hoped that institutions such as the American College of Physical Therapy are but a passing phase. . . ."

As far as this Bureau can determine, it was in 1937 that Winters started using the postcard announcements of his courses. They are frequently given at the Hotel Morrison in Chicago and in other cities scattered through the United States—Cincinnati, Pittsburgh, Philadelphia, St. Louis, Kansas City, Des Moines, New York, Denver, Omaha. He frequently makes return visits. For example, in 1939 he gave a course in Columbus, Ohio, on April 16 and 17 and in Cleveland April 18 and 19, and in 1941 he gave courses in Columbus on June 15 and 16 and in Cleveland on the 17th and 18th.

The card which he forwards announces a "Condensed Postgraduate Course," which is described as a "practice class in ambulant therapy." It is stated on the cards that "Dr. Winters needs no introduction to the profession—his work is nationally recognized, and he has conducted many similar courses." The card goes on to announce the treatment of hernia by injection, discusses everything from low back pain to sinus disease and impotence and describes the tuition as $10 for four sessions.

Shortly after the receipt of these cards in any locality, numerous inquiries are made of the Bureau of Investigation concerning the qualifications of Winters. The inquirers are informed that Winters was born in 1901 and graduated from Loyola University School of Medicine, Chicago, in 1928, that he is not a member of the Chicago Medical Society or a Fellow of the American Medical Association and that no information is available to show that he has had special training in any field of surgery.

Only rarely today does one encounter the itinerant physician who goes about from city to city, maintaining temporary offices in hotels. Frequently pseudomedical lecture courses are given to laymen by faddists and others. Winters, however, is a Doctor of Medicine who is licensed to practice in Illinois and advertises his courses exclusively, so far as the Bureau has been able to determine, to physicians. No information is available concerning the exact nature of the courses given. It is not customary—to put it mildly—for reputable physicians to engage in such activities. Time and time again the information on Winters has been forwarded at once from this Bureau but received only after he has left for other cities. An example of this occurred in 1938, when information concerning him was forwarded to the *New England Journal of Medicine* and printed in its December 1 issue with the following notation: "The above letter was received too late for publication in the November 24 issue of the *Journal*. Dr. Winters' postgraduate course has been given; we wonder how many New England physicians were gullible enough to attend."

The time has long since passed when there could be any reason for a lecturer to visit physicians and surgeons in their own localities in order to inform them of new technics, even if it was done in an ethical manner. The attendance at such meetings as those of the American Medical Association, the American College of Surgeons, the American College of Physicians and the various specialty societies and, more particularly, at various ethically conducted postgraduate courses in institutions approved for giving such courses indicates clearly that, busy as he is, the physician who realizes the need of additional training does not find it difficult to obtain this training.

THE WALKER-MANOLA NOSTRUMS

Persistence of a Line of St. Louis Products

The Walker Pharmacal Company and the Manola Company, 4200 Laclede Avenue, St. Louis (apparently subsidiaries of the Luyties Pharmacal Company of the same address), continue to bombard the medical profession with advertising for such nostrums as Manola (Manola Company) and Hymosa, Phytoline and Succus Cineraria Maritima (Walker Pharmacal Company). This line of nostrums has been on the market for more than a quarter of a century and comments on the various products have appeared from time to time in THE JOURNAL.[1] More than fifteen years ago THE JOURNAL (Jan. 16, 1926, page 220) pointed out that Manola, previously found (1910) to be a wine fortified with alcohol and a slight amount of added medicinal substances, was exploited as a "tonic, reconstructive, and tissue builder." It had been taken out of the class of homeopathic nostrums according to the formula published at that time, which indicated the presence of $\frac{1}{120}$ grain (0.0005 Gm.) of strychnine phosphate and ¼ minim (0.016 cc.) of solution of potassium arsenite in the maximum recommended dose. Concerning the Walker preparations, the same note pointed out that Hymosa had been found to be essentially a solution of salicylates exploited as a remedy for rheumatism; that Phytoline, a preparation of pokeberry juice, was advertised as a "Powerful Anti-Fat," and that claims for Succus Cineraria Maritima, recommended for use in cataract, were made *in the firm's advertising* to evade the Food and Drugs Act, under which it had previously (1916) pleaded guilty to the charge of false and fraudulent claims *on the label* for this product.

Despite the repeated condemnation of these nostrums by THE JOURNAL on behalf of the medical profession and the elimination of unwarranted claims from the labels through the efforts of

1. Unpaid Peddlers of Secret Nostrums, Pharmacology, J. A. M. A. **44:** 1462 (May 6) 1905. The Composition of Manola, Pharmacology, J. A. M. A. **54:** 1154 (April 2) 1910. Manola—Physicians as Unpaid Peddlers of Nostrums, Propaganda for Reform, J. A. M. A. **60:** 1092 (April 5) 1913. Succus Cineraria Maritima, Propaganda for Reform, J. A. M. A. **68:** 864 (March 17) 1917. Succus Cineraria Maritima and Phytoline, Queries and Minor Notes, J. A. M. A. **83:** 2041 (Dec. 20) 1924. Manola—Hymosa—Phytoline—Succus Cineraria, Queries and Minor Notes, J. A. M. A. **86:** 220 (Jan. 16) 1926. Succus Cineraria for Cataract, Queries and Minor Notes, J. A. M. A. **89:**1446 (Oct. 22) 1927. Succus Cineraria Maritima in Cataract, Queries and Minor Notes, J. A. M. A. **99:** 326 (July 23) 1932.

the Food and Drug Administration, the promoters apparently still find it profitable to make such claims in advertising to the medical profession.

Manola, referred to in the firm's recent form letter as "The Standard Tonic of the Medical Profession," is still promoted as a "Reconstructive Tonic," but now contains such "indispensable nutriments" as minerals and vitamin B_1, as indicated by the following published "quantitative formula":

Each ounce of Manola contains: Concentrated Solution of Combined Glycerophosphates of Iron, Lime, Magnesium, Sodium and Potassium, 16 min.; Nux Vomica, Tr., U. S. P. (represents Strychnia .0029 gr.), 2½ min.; Cinchona Alkaloids (representing Tr. Cinchona 2 min.); Lactic Acid, 1½ min.; and 200 International Units Vitamin B_1.

Manola with vitamin B_1 is claimed to be of "unquestionable value in Reconstructing Disease Resistance." The Manola Company also markets "a new companion product," Vitamanola, in tablet form. Whereas previously the firm offered two 4 ounce free samples of Manola to physicians, it now offers instead one 4 ounce bottle of Manola liquid with vitamin B_1 and 100 tablets of Vitamanola. No doubt such generosity is well repaid by those gullible physicians who follow the firm's suggestion that either the original full size bottle of Manola be prescribed or the patient be directed to purchase it directly from the druggist to avoid the necessity of prescribing. The use of "tonics" and "shotgun formulas" has long been abandoned by scientific medicine.

Succus Cineraria Maritima (Walker) is now advertised in a booklet entitled "Cataract and the General Practitioner," in which it is still claimed that "Local Treatment May Prevent Operation In Cataract." Under the heading "Other Reliable Products" the booklet contains a list of the firm's other nostrums, including Hymosa and Phytoline for rheumatism and obesity respectively. Such an array of nostrums is an insult to the intelligence of qualified members of the medical profession. Surely it is not too much to hope that the support which the promoters of such products may receive from prescribing physicians shall one day be withdrawn.

SOME MISCELLANEOUS FRAUD ORDERS

United States Post Office Closes the Mails to Certain Medical Fakes

Fraud orders issued by the Post Office Department have frequently been the subject of extensive articles by the Bureau of Investigation in these pages of THE JOURNAL. Following are brief abstracts of some Fraud Orders not dealt with previously:

"Dr." F. C. A. Meyer Concerns.—On Dec. 4, 1940 the Post Office issued a fraud order against "Dr." F. C. Adolph Meyer, who did business under his own name as well as Dr. F. C. A. Meyer Institute, Vegetarian Foods Co., Dr. F. C. A. Meyer Co., Naturopathic Institute and Meyer's Publications, at Pewee Valley, Ky. From another source it was reported in 1937 that Meyers was running at Pewee Valley something he called the "Natural Pathic Institute." Meyer sold through the mails a nostrum known as "Christian's Red Salt." According to government chemists, Christian's Red Salt consisted of over 93 per cent of common salt with minute amounts of other minerals. Yet Meyer claimed it could make high blood pressure disappear and would eliminate prostatic disorders, stomach and nerve troubles and restore lost "vim" and "pep." The Post Office produced evidence that these amounted to false and fraudulent pretenses, representations and promises. In September 1939 F. C. A. Meyer, advertising his "naturopathic" services, sent an inquirer a peculiarly composed letter which included such statements as "I work about the head with fomentations, vibrators and oneway electric currents in the proper directions with emmidiate [sic] results as to strength . . ."

Orofood Company.—This New York business apparently was started by one Christopher Von Chlingensperg, who, later going to Germany and being unable to return because of conditions there, was said to have been succeeded as manager in 1939 by a Dr. Frank G. Bass, who cannot be identified as a physician in the American Medical Association's files. This concern sold "Orofood," representing that it would prevent or overcome pyorrhea, decay or loss of teeth, remedy pink tooth brush, and restore dull, yellow, decaying teeth to a sound, healthy, white, sparkling condition. One specific claim was that "Orofood is the result of 15 years of research work and is compounded to help to build and maintain your oral cavity in perfect condition. Fluorcalcium, Phosphorus, Magnesium, Potassium, Sodium, Manganese, Sulphur, Iron, and last but not least, Silicon and Iodine besides others in minute quantities, all these minerals in proper cooperation with Vitamins A, B, D etc. enable the blood to keep you healthy with healthy teeth, nails, hair and bones in general. Orofood also contains STAPHISAGRIA, an herb known to be of benefit in oral conditions." Government chemists found that the nostrum contained lactose, flour, soya bean flour, yeast cells, cereal starch, and minute amounts of calcium and phosphorus. The Post Office declared the "cure" to be a fraud and on Feb. 1, 1940 issued an order debarring it from the mails.

Rhein Gold Herb Tea Co.—Portland, Ore., was the address of this business, run by a Mae Rockwell. In her advertising Miss Rockwell offered through the mails to analyze specimens of urine and "without guesswork" determine the state of the customer's health and prescribe certain preparations to overcome, cure or correct the symptoms and diseases that these urinalyses disclosed. Further, the seller was charged with falsely and fraudulently representing that "Rhein Gold Tea Preparations" known as "Nos. 1, 13, 1425 and 1430," and "Dulse," when taken as directed, would remove the causes of malnutrition, digestive troubles, carbuncles, leg sores and constipation due to bowel strangulation. It was shown that a customer who twice under assumed names sent in specimens of faked urine and mentioned certain alleged symptoms was told that he was suffering from serious conditions (which he did not have) and advised to order certain preparations from the company. He did so and the government chemists reported on the first lot as follows: "Tea No. 1," coarsely ground herbs, chiefly equisetum stems, couch grass, uva ursi and mint leaves, and seeds of cleavers; "Tea No. 13," coarsely ground herbs, principally senna leaves, uva ursi leaves, anise seed and clover flowers; "No. 1425," in each tablet, by grains, ferrous carbonate 0.86, magnesium sulfate 1.38, sodium sulfate 0.04, arsenic 0.0095 and strychnine 0.0065; "No. 1430," per capsule, by grains, potassium iodide 6.95, magnesium oxide 0.4, calcium carbonate 0.13 and powdered savin; "Dulse," dried ground thallus material resembling a species of Rhodymenia. The second lot of medicines included, besides the "No. 1 Tea" and the "No. 13" mentioned, "Uterine Tablets" and "1440 Nerve Tea." The tea, it was said, if taken as directed, would supply about 40 grains of potassium iodide daily and in such doses of the drug would be almost certain to produce iodine poisoning, with such symptoms as nausea, skin rashes, dizziness and excess flow of mucus from nasal, salivary and other glands. The composition of the Uterine Tablets was not reported. Expert medical testimony showed that not one of the ingredients in any of these preparations was a specific or cure for the symptoms and diseases outlined by the promoter in his alleged diagnoses of the two test cases mentioned (except that senna will temporarily relieve constipation if present) or provided effective treatment for diabetes or syphilis, which the customer represented that he had. The Post Office therefore declared the business to be a scheme for obtaining money fraudulently through the mails and on Oct. 25, 1940 issued a fraud order against the Rhein Gold Herb Tea Co. and its officers and agents.

R. G. Wilborn.—This Los Angeles person sold by mail numerous "formulas," medical and otherwise, and some articles and "secrets." He offered a "Magic Rubbing Cloth for all aches and pains, secret, $1"; a "Pyorrhea Remedy, $1" and a "Simple treatment for catarrh, varicose veins, gall stones, headache, all 4 treatments, $2." Then there was his "SEX ENERGY PRODUCING FOOD LIQUID (Formula) Prepared easily and inexpensively at home. Only two simple ingredients needed. No drugs. Most beneficial to build vigorous manhood. Complete 300 words of directions only 50c." Also, you could get "formulas" for dandruff lotion, liniment, spring tonic, rheumatism and wrinkles. Accompanying these formulas was more circular matter soliciting remittances for such "secrets" as "How to Gain Weight Easily and Naturally Without Diet or Drugs," "How to Stop the Liquor Habit," "How to Make a Vitality 'Pep' Cocktail," "How to Quit the Tobacco Habit" and "The Japanese Remedy for Appendicitis." Finally, there was "Formula No. 29," a skin peel, which Wilborn represented would produce in three days a "new skin" that would be "clear, smooth, youth like or beautiful, regardless of the age or physical condition of the user." It was to this that the Post Office investigators paid most attention in looking into Wilborn's scheme. One was told to mix 1 part of resorcin, 3 parts of alcohol and 4 drops of perfume to each ounce, and paint the face with this mixture, which was not only for face peeling but also for tan, freckles, wrinkles, enlarged pores, pimples and blackheads. Expert medical evidence introduced at the Post Office hearing showed that though this preparation would peel the skin from the face it could not remove or correct enlarged pores, pimples, blackheads or wrinkles and hence constituted a fraud on the public. Wilborn was found to be a clerk for a wholesale drug house, conducting his mail order business in an unkempt shed behind his home. He also offered "secrets" on "Playing Slot Machines for Profit," "Winning on Marble Games of all Kinds" and "A Dice System That Will Beat Any Fair Dice Game." On Dec. 18, 1940 the Post Office issued a fraud order closing the mails to his schemes.

Tropical Products Co.—This Chicago concern, started around 1937 by a Walter Krah, put out a laxative, "Tropix," representing that it would restore the "eliminative tract" of constipated persons to "normal functioning," could prevent and overcome any case of constipation and prove entirely different from other laxatives, harmless to any user and effective for any case of "stomach distress." Further, the advertising claimed that it was a "wonderful, new, natural product" which, though intended to prevent or cure constipation, did not "work like a laxative." Also there was the usual "guarantee of complete satisfaction or money refunded." The label declared that Tropix was "composed only of sun-dried, powdered, tropical fruits, Algaroba, Pudding Tree Fruit, Papaya," and this claim was confirmed by a government microanalyst, who added that pudding tree fruit is also known as cathartocarpus, cassia fistula or purging cassia. Tropix was to be sprinkled over cereals or fruit, mixed with fruit or vegetable juices, milk or cocoa, or taken in plain water. Expert medical testimony introduced at the hearing by Post Office authorities showed that Tropix was essentially a laxative because of its cassia content but that it also might have some slight digestive action because of the presence of papaya, which contains some enzymes. The expert testimony brought out, however, that Tropix will not and cannot restore the "eliminative tract" of constipated persons to normal and, in fact, by irritating it, may aggravate the factors involved. The testimony further pointed out that Tropix will not and cannot benefit "stomach distress" (aside from its slight digestive action) and that the use of a laxative (such as Tropix) in those cases of "stomach distress" that involve ulcer or appendicitis is unsafe and may result in loss of life. As the sale of the stuff was found to constitute a swindle conducted through the mails, the Post Office on Sept. 11, 1940 issued a fraud order against Tropical Products Company and its officers and agents.

Correspondence

WASSERMANN TESTS AND VACCINATION

To the Editor:—In a communication to THE JOURNAL (Aug. 10, 1940, p. 475) commenting on my report of a patient whose blood showed a series of positive reactions for syphilis following successful vaccination for variola (*Illinois M. J.* **77**:78 [Jan.] 1940) Drs. A. P. Bay and M. I. Sankstone stated that I had attributed this effect to vaccinia. I am sorry that this imputation should have been drawn from my report, which merely recorded the observations. It is not proper to draw conclusions from the report of a single case of this type. Nor can the conclusions of Drs. Bay and Sankstone that because they had examined 100 serologically negative persons both before and after vaccinia inoculation with negative results be held to minimize the importance of this type of vaccination as a source of error in the presumptive blood serologic reactions for syphilis.

Considering what has been known since 1938 of the comparatively low incidence of positive reactions, both false and valid, in the general population and for that matter of the active type of the disease portended itself in this generation, the probabilities of "less than 1 per cent" as deduced by Drs. Bay and Sankstone from their study on the incidence of false positive reactions on the basis of vaccination not only lose all significance but may serve to disguise the true picture. The entire series was not sufficiently large to evaluate probabilities, and mention is not made of the percentage of takes. In the case which I reported, vaccination was successful.

The serologic tests for syphilis have always been regarded as being more reliable in their positive than in their negative phases. In the presumptive tests the positive reactions are the important ones, and the total of all positive reactions in any group may be decidedly less than 1 per cent. To be placed within its proper order of magnitude, the evaluation of the incidence of false positives must be on the basis of the percentage of the total positive reactions in any particular series. When this is done, the thesis of the opening sentence of this paragraph is brought to question. In that manner two more questions are raised: What percentage of positive serologic tests sufficiently persistent to lead to the institution of therapy are actually false reactions and what percentage of these false reactions in turn are due to some particular recognizable artefact such as vaccination with vaccinia must be of interest to the physician and to the "less than 1 per cent" patient who may be 100 per cent out of luck for the duration of the unnecessary treatment or for the rest of his life?

To some extent all these questions might find their answer in the recent report of Thomas and Garrity (*U. S. Nav. M. Bull.* **39**:272 [April] 1941). Their findings are of tremendous importance even though they may reflect an unusual situation in that the authors secured vaccination lesions in about half of the group vaccinated prior to the conduct of the Kahn test. Among 20,000 naval recruits there were 73 positive tests returned, an incidence of 0.365 per cent. (This compares to my own figures compiled between 1937 and 1940 of 4 positive reactions among 1,116 male college students of about the same age and geographic distribution as the naval recruits.) Of the 73 positive reactions, 32 (44.9 per cent) proved to be false positives, though 8 additional subjects in the persistently positive group were classified as exceedingly doubtful with respect to having or having had the disease in any form. For the Kahn test on the first series of 10,000 subjects the blood was drawn after they had been vaccinated; in the second series of 10,000 additional subjects the blood was taken before the recruits were inoculated with the cowpox vaccine, a policy which the authors have now instituted as routine and which certainly seems to be a wise one when the results in the two groups are considered. The first group showed 81.2 per cent of all adjudgedly false positive reactions: 26 out of 32. One case which the authors cited in detail shows a striking parallelism to that which I reported. The authors state that the findings suggest a definite relationship between cowpox vaccination and the false positive Kahn reaction, and this conclusion seems warranted from their findings, particularly when it is brought out that, of the false positive reactions in the first series, 89 per cent occurred in the successfully vaccinated group. What must be emphasized is that an analysis of these data would indicate that 56 per cent of all false positives in the entire series might be attributed to the preceding vaccinations.

The report of Thomas and Garrity must redirect attention to the fact that recent successful variola vaccination is a definite source of error in the blood serologic tests for syphilis. I say redirect, because the fact appears to be well known to the experienced physician who was in practice when there was plenty of syphilis and before the incidence of all except the congenital and remotely acquired types had started their trend toward the present vanishing point. Both Dr. D. V. Omens and the late Dr. Bernard Fantus, who examined the patient on whom I reported, were certain that the fact was such common knowledge that it must have been reported several times over. It was only after a search of the literature had showed that it was not, after syphilis had been ruled out in this patient as far as was humanly possible and after an interval of twelve months during which there were no clinical manifestations and the serologic tests remained negative, that my own report was rendered.

ROBERT D. BARNARD., M.D., Chicago.

[ED. NOTE.—This letter was received and put in type before the article by Lynch, Boynton and Kimball was published in THE JOURNAL, Aug. 23, 1941.]

SPECIMENS OF THE EAR, NOSE AND THROAT IN THE ROYAL COLLEGE OF SURGEONS, LONDON

To the Editor:—Although known and valued by ear, nose and throat workers, it has hardly been appreciated that London possessed perhaps the largest and most valuable collection of museum specimens connected with the ear, nose and throat.

The museum of the Royal College of Surgeons had, for many years, been assembling a select number of pathologic, anatomic and physiologic specimens concerned with this department. One of the earliest gifts of normal anatomy arrived when Toynbee presented his three hundred specimens of temporal bones. This addition was greatly enriched when Arthur Cheatle handed over to the museum his series of sectioned temporal bones. The basis of the group of specimens related to rhinology was formed when the large collection of Onodi, from Budapest, was secured and presented by the otolaryngologists of this country. A valuable addition was made when V. E. Negus made a gift of all the specimens which had formed the foundation of his well known study on the comparative anatomy and physiology of the voice. This last addition escaped much damage when the museum suffered considerably during London's bombardment by the Nazis in May last.

Owing to the dispersal, for greater safety, of the specimens that were undamaged, it has not yet been possible for the college authorities to draw up and publish a complete and reliable statement of the loss to medical science suffered by the museum from enemy action. So far as the department of the ear, nose and throat is concerned, the following information has been made known:

Since the catalogs of the museum have been preserved, it will be possible in the future to reproduce many specimens of

normal anatomy from fresh preparations. The Onodi collection of the anatomy of the nose and accessory sinuses was damaged, but about ninety-five specimens are intact and the others, being of normal, human anatomy, can in time be replaced. The Toynbee and Cheatle collections have suffered more severely. It is hoped that, after the war, some young aural surgeons will be forthcoming to recreate the Toynbee and Cheatle series of temporal bones. As to the pathologic specimens, it is not possible to give a full report at present.

It is interesting and comforting to recall that the fourteen specimens of the anatomy of the paranasal sinuses recently presented by the late Professor Hajek are complete and intact. Professor Hajek was able to escape from Vienna about two years ago, and with the generous help of American and British colleagues he reached London with his devoted wife, a sister of the well known dramatist Schnitzler. Here, with the help of his confrères, he was able to spend the last two years of his life in modest but comfortable conditions and in the enjoyment of the liberty which he so much appreciated. When he made his escape from Vienna he was allowed to bring with him, in money, the equivalent of only 10 shillings. He and his wife had to produce and leave behind their gold watches. The only pieces of gold that they were allowed to export were their wedding rings. In spite of these difficulties he managed to bring away with him 14 specimens of his valuable collection of rare abnormalities of the anatomy of the nasal sinuses. The rest of his 150 specimens had to be left in Austria. These 14 formed part of the specimens which he had shown, during nearly fifty years, in the practical classes which the American editors of his well known book (Pathology and Treatment of the Inflammatory Diseases of the Nasal Accessory Sinuses, London, Henry Kimpton, 1926) deservedly called "famous." They are illustrated in that work which these translators of the English edition referred to as "a recognized classic."

As a token of his gratitude for his deliverance from the city where he had so long been one of the most esteemed teachers in the faculty of medicine and of the welcome he had received in London, Hajek presented these unique specimens to the Royal College of Surgeons, through Mr. T. B. Layton, the honorary curator and cataloguer of the Onodi collection. It is one of life's ironies, and it is some comfort to remember it, that when the Nazi bombs were doing so much damage to the science and teaching of surgery in London they missed some of the most valuable specimens in otolaryngology which had come originally from Vienna and from Budapest.

ST. CLAIR THOMSON, M.D., London, England.

THE CAUSTIC ACTION OF SODIUM SULFATHIAZOLE

To the Editor:—In THE JOURNAL, April 26, in an article on "chronic sinusitis," F. M. Turnbull recommends the use of 5 per cent sodium sulfathiazole for local treatment. As a result, many general physicians and ear, nose and throat specialists are being requested to use this drug in the treatment of chronic as well as acute sinusitis. The following report indicates that the local use of sodium sulfathiazole, or in fact the use of any sodium salt of sulfanilamide, may be extremely dangerous in the treatment of sinusitis:

A woman had a foul purulent infection in the left antrum following the extraction of a tooth. There was some osteomyelitis in the area of the tooth socket, where there was a fistula. The teeth adjacent to the fistula were loose and the bone about the roots was involved. There was a large, loose sequestrum in the fistula. The discharge was extremely foul. The exodontist was afraid that he would stir up a more extensive process if any further operative procedure was done.

Since frequent irrigations of the antrum did not benefit her, sodium sulfathiazole was tried. After the sinus was washed out with physiologic solution of sodium chloride 5 cc. of 5 per cent sodium sulfathiazole was instilled. The following day the patient reported that there seemed to be less foul discharge and that she felt much better. Three days later 10 per cent sodium sulfathiazole was instilled. The washings seemed to be definitely clearer and were less foul. Subsequent washings were almost clear, although some black specks of material were washed out. The solution came out through the normal ostium into the nose, as well as out through the fistula into the mouth. During the next three weeks the sulfathiazole solution was instilled ten times. Following this, the discharge again seemed more foul and small spicules of bone were taken out of the tooth socket. The sequestrum above the fistula became more loose, and it was decided that it was time to remove the two teeth next to the fistula as well as the sequestrum.

The removal of the teeth and the large sequestrum made a large opening into the antrum, which was filled with a black appearing material that had the consistency of clay. Some of this material was scooped out and the rest of it was washed out with a syringe. No normal tissue or lining was seen. The patient had an uneventful convalescence.

The only variation in the treatment and operation from that in other cases in past years was the use of the sodium sulfathiazole. Dr. M. L. Tainter of the Pharmacology Department of Stanford University School of Medicine said that this condition had probably been caused by the excessive alkalinity of the solution employed.

The sodium salts of the sulfanilamide group are extremely alkaline, having a p_H which ranges from 10 to 11. This is about the same alkalinity as arsphenamine and it is well known that arsphenamine, because of its alkalinity, causes necrosis when it gets outside the vein. A solution as strongly alkaline as this is extremely caustic, and what happened in the antrum in this case was simply that the sodium sulfathiazole charred or burned the granulation tissue and entire lining of the antrum. The fact that each time it was instilled it ran out immediately through the nose and fistula is probably the reason more serious complications did not result, including destruction of bone. There have been scattered references of severe local irritation of tissues and mucous membranes in the literature, but these apparently have not attracted sufficient attention.

Fortunately, the chief use of this drug locally was advocated in the form of a spray, which would introduce only a small amount into the nose. The protective coating of mucus over the surface of the nose has probably been the reason why this drug has not caused a great deal of damage.

The sodium salts of the sulfanilamide group are so caustic that they may do irreparable damage if they are instilled into the tissues, sinuses or any body cavity such as the pleural or peritoneal spaces.

RUSSELL FLETCHER, M.D., San Francisco.

"CUTIS ANSERINUS," OR "GOOSE PIMPLES"

To the Editor:—May I be permitted to differ with Dr. Buck of Boston on the term "goose flesh," "goose bumps" or "goose pimples?" The time honored Latin for this condition is "cutis anserinus" which methinks should be translated "goose skin," not "flesh."

H. L. BAPTIST, M.D., Ivy Depot, Va.

To the Editor:—Dr. R. W. Buck's expressed intellectual "allergy" for "goose pimples," slang variant for "goose flesh" (THE JOURNAL, August 30), is nothing to my own "goose flesh" whenever I hear some surgeon say "I operated her."

WALTER A. LANDRY, M.D., Chester, Pa.

Council on Medical Education and Hospitals

CONTINUATION COURSES FOR PRACTICING PHYSICIANS

For a number of years the Council on Medical Education and Hospitals has collected and published data concerning the various types of continuation courses that have been offered to practicing physicians. Following is a list of the continuation courses which will be available during the fall quarter of 1941 and it is the intention of the Council to prepare and disseminate similar information at intervals of three months. Such advance notice of graduate courses will be of value to physicians who may be planning to take some postgraduate work but who at present have no convenient means of knowing when and where the subjects in which he is interested will be taught.

The space available in THE JOURNAL this week does not permit publication of the entire list of courses; the remainder of the list will be published next week.

WILLIAM D. CUTTER, M.D., Secretary.

Continuation Courses for Practicing Physicians, Fall of 1941

Institution	Courses Scheduled to Begin	Length and Content of Course	Number of Students Accepted for Each Course	Registration Fee and/or Tuition	For Detailed Information Write to
ALLERGY					
Tufts Medical School, Postgraduate Division	Oct. 20	5 days	6 or more	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Columbia University College of Physicians and Surgeons	Oct. 27	3 mornings, 1 afternoon a week, 8 weeks	.....	$75	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Dec. 1	3 weeks, full time	4-8	$150	
ANATOMY					
College of Medical Evangelists.....	Oct. 5	3 to 10 hours; elective subcourses	.....	$5 to $15	Chairman, Committee on Postgraduate Education, 312 N. Boyle Ave., Los Angeles
University of Illinois College of Medicine	Arranged on application	Variable	4 or more	$75 a semester plus cost of materials	Assistant to the Dean, University of Illinois College of Medicine, 1853 W. Polk St., Chicago
Woman's Medical College of Pennsylvania	Sept. 17	8 month course	2	$100 to $300	Dean, Woman's Medical College of Pennsylvania, Henry Ave. and Abbottsford Rd., Philadelphia
ANESTHESIA					
Harvard Medical School, Courses for Graduates	Arranged on application	1 month	3	$30 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Tufts Medical School, Postgraduate Division	Dec. 1	4 days	4-10	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Kings County Hospital, Brooklyn (Joint Committee on Post-Graduate Education)	Oct. 8	2 afternoons a week, 8 weeks	8	$35	Registrar, Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn
Columbia University College of Physicians and Surgeons	Arranged on application [2]	2 or 3 weeks, full time	.....	$100 to $150	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
New York Polyclinic Medical School and Hospital	Arranged on application	6 week and 3 month courses	.....	$150 to $300	Medical Executive Officer, New York Polyclinic Medical School, 335 W. 50th St., New York City
New York University College of Medicine	Dec. 1	3 weeks, full time	5	$150	Assistant Dean, New York University College of Medicine, 477 First Ave., New York City
Woman's Medical College of Pennsylvania	Sept. 17	8 month course	2	$100 to $300	Dean, Woman's Medical College of Pennsylvania, Henry Ave. and Abbottsford Rd., Philadelphia
ARTHRITIS					
Columbia University College of Physicians and Surgeons	Oct. 13	5 days	4 or more	$35	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
BACTERIOLOGY					
Columbia University College of Physicians and Surgeons	November	1 month, full time	2	$100	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	January	1 month, mornings	3-8	$50	
CARDIOLOGY					
Los Angeles Heart Association.....	Nov. 4	2 days	.....	$5	Chairman, Program Committee, 1136 W. 6th St., Los Angeles
Hospitals in San Francisco (San Francisco Heart Committee)	Oct. 30	3 days	.....	$15	Program Chairman, Post-Graduate Symposium, Room 407, 277 Pine St., San Francisco
Hospitals in Emporia, Kan.....	October	5 days	.....	$15	Executive Secretary, Kansas Medical Society, 112 W. 6th St., Topeka
Tufts Medical School, Postgraduate Division	Nov. 17	6 days	.....	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Jewish Hospital, Brooklyn (Joint Committee on Post-Graduate Education)	Oct. 7	3 mornings a week, 5 weeks (includes applied electrocardiography)	12	$20	Registrar, Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn
Kings County Hospital, Brooklyn (Joint Committee on Post-Graduate Education)	October	10 sessions on heart disease in childhood	8	$10	Registrar, Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn
Columbia University College of Physicians and Surgeons	Oct. 27	8 weeks, 2 mornings a week; afternoon bedside clinics (heart diseases in adults)	5-12	$50 and $25	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
DERMATOLOGY AND SYPHILOLOGY					
Harvard Medical School, Courses for Graduates	December	1 month, mornings	Limited	$40 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Tufts Medical School, Postgraduate Division	Jan. 19	6 days	6	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Columbia University College of Physicians and Surgeons	Oct. 3; on arrangement	7 months, weekly lecture; 6 week and 3 month clinical courses, 2 or 3 days a week	.....	$40 to $100	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Oct. 1 [2]	7 months, variable hours (basic sciences in dermatology)	.....	$75	

References will be found on page 1208.

Continuation Courses for Practicing Physicians, Fall of 1941—Continued

Institution	Courses Scheduled to Begin	Length and Content of Course	Number of Students Accepted for Each Course	Registration Fee and/or Tuition	For Detailed Information Write to
DIABETES					
Tufts Medical School, Postgraduate Division	Jan. 19	6 days	.....	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Columbia University College of Physicians and Surgeons	Nov. 17	5 days	4 or more	$35	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Dec. 1	5 days (therapeutics)	4 or more	$35	
Graduate School of Medicine, University of Pennsylvania	Arranged on application	2 to 4 weeks	.....	$150	Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia
ELECTROCARDIOGRAPHY					
Tufts Medical School, Postgraduate Division	Jan. 26	3 days (advanced electrocardiology)	.....	$20 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Columbia University College of Physicians and Surgeons	Oct. 6	5 days	4 or more	$50	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
ENDOCRINOLOGY					
Tufts Medical School, Postgraduate Division	Nov. 10	5 days	.....	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Jewish Hospital, Brooklyn (Joint Committee on Post-Graduate Education)	October	10 sessions	4	$20	Registrar, Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn
Kings County Hospital, Brooklyn (Joint Committee on Post-Graduate Education)	Oct. 21	3 weeks, twice a week (metabolic disease)	8	$10	
FORENSIC MEDICINE					
New York University College of Medicine	October	1 to 8 months (various courses)	.....	$25 to $100	Assistant Dean, New York University College of Medicine, 477 First Ave., New York City
GASTROENTEROLOGY					
University of Chicago, The School of Medicine	Arranged on application	2 week and 3 month courses in gastroscopy	.....	$100 to $150	Dean of Students, University of Chicago, The School of Medicine, Chicago
Columbia University College of Physicians and Surgeons	Oct. 27	3 mornings, 1 afternoon a week, 8 weeks	.....	$75	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Arranged on application [2]	3 afternoons a week, 2 months (gastroscopy)	1	$200	
New York Polyclinic Medical School and Hospital	Jan. 2	6 weeks	.....	$75 to $100	Medical Executive Officer, New York Polyclinic Medical School, 335 W. 50th St., New York City
Graduate School of Medicine, University of Pennsylvania	Arranged on application [2]	16 weeks	.....	$400	Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia
University of Virginia Department of Medicine	Nov. 14	2 days	.....	None	Chairman, Graduate Clinics, University of Virginia Department of Medicine, University
GYNECOLOGY					
University of Illinois College of Medicine	Arranged on application	Obstetrics and gynecology in preparation for American Board exams.	.....	Varies	Assistant to the Dean, University of Illinois College of Medicine, 1853 W. Polk St., Chicago
Harvard Medical School, Courses for Graduates	Oct. 13	3 mornings a week, 1 to 3 months	4	$25 to $50 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Columbia University College of Physicians and Surgeons	October	Various courses throughout year	Limited	Varies	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
New York Polyclinic Medical School and Hospital	Arranged on application	6 weeks	.....	$75	Medical Executive Officer, New York Polyclinic Medical School, 335 W. 50th St., New York City
Woman's Medical College of Pennsylvania	Sept. 17	8 month course	2	$100 to $300	Dean, Woman's Medical College of Pennsylvania, Henry Ave. and Abbottsford Rd., Philadelphia
HEMATOLOGY					
Tufts Medical School, Postgraduate Division	Nov. 17	6 days	.....	$25 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Columbia University College of Physicians and Surgeons	Oct. 27	2 afternoons a week, 8 weeks (advanced clinical hematology)	6	$50	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
LARYNGOLOGY					
Harvard Medical School, Courses for Graduates	October; on arrangement	6 months clinical; 5 sessions, surgical	5	$50 to $75 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Graduate School of Medicine, University of Pennsylvania	Arranged on application	10 days (operations on cadaver)	.....	$150	Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia
MEDICINE—General Medical and Surgical Subjects					
University of Arkansas School of Medicine	Oct. 22	2 days	.....	$5	Chairman, Committee on Postgraduate Instruction, 701 Main St., Little Rock
Tulane University of Louisiana School of Medicine	Oct. 20	6 days	.....	$5	Director, Department of Graduate Medicine, Tulane University of Louisiana School of Medicine, 1430 Tulane Ave., New Orleans
	Jan. 5	6 to 12 weeks	.....	$150 to $225	
Medical Society of New Jersey.....	Dec. 3	1 day	.....	None	Executive Officer, Medical Society of of New Jersey, 143 E. State St., Trenton
International Medical Assembly, Minneapolis	Oct. 13	7 days	.....	$5	Managing Director, International Medical Assembly, 16 N. Carroll St., Madison, Wis.
Kansas City Southwest Clinical Society, Kansas City, Mo.	Oct. 6	4 days	.....	$5	Executive Secretary, Kansas City Southwest Clinical Society, 208 Shukert Bldg., Kansas City, Mo.

References will be found on page 1208.

Continuation Courses for Practicing Physicians, Fall of 1941—Continued

Institution	Courses Scheduled to Begin	Length and Content of Course	Number of Students Accepted for Each Course	Registration Fee and/or Tuition	For Detailed Information Write to
MEDICINE—General Medical and Surgical Subjects—Continued					
Lincoln Hospital, Durham (Division of Cooperation in Education and Race Relations)	Oct. 8	1 day	.....	$5	Dr. David T. Smith, Duke Hospital, Durham
Duke University School of Medicine	Oct. 16	3 days	.....	None	Dr. L. D. Baker, Duke Hospital, Durham
Oklahoma City Clinical Society....	Oct. 27	4 days	.....	$10	Executive Secretary, Oklahoma City Clinical Society, 512 Medical Arts Bldg., Oklahoma City
Germantown Dispensary and Hospital, Philadelphia	Dec. 3	3 days	.....	None	Director of Laboratories, Germantown Hospital, E. Penn and Wister Sts., Philadelphia
Dallas Southern Clinical Society....	Oct. 27	3 days	12	$10	Dallas Southern Clinical Society, 1127 Medical Arts Bldg., Dallas
Post Graduate Medical Assembly of South Texas	Dec. 2	3 days	.....	$10	President, Post Graduate Medical Assembly of South Texas, 229 Medical Arts Bldg., Houston
MEDICINE, INTERNAL					
University of California Medical School	Jan. 5	3 days (drug therapy)	.....	$20	Director of Refresher Courses, c/o Dean's Office, University of California Medical School, San Francisco
Harvard Medical School, Courses for Graduates	October; November	1 month	.....	$150 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Tufts Medical School, Postgraduate Division	Oct. 6	4 weeks	.....	$50 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Bellevue Hospital (New York University College of Medicine)	First day of month	1 month, mornings	6 to 12	$50	Director, Fourth Medical Division, Bellevue Hospital, 26th St. and East River, New York City
Columbia University College of Physicians and Surgeons	Jan. 5	1 or 2 months, full time	4 to 10	$125 to $200	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Jan. 19	2 weeks, full time (diagnostic procedures)	4 to 10	$50	
New York Polyclinic Medical School and Hospital	Arranged on application	6 weeks, full time	.....	$100	Medical Executive Officer, New York Polyclinic Medical School, 335 W. 50th St., New York City
Hahnemann Medical College and Hospital	Oct. 1	1 month to 1 year	.....	Varies	Head of the Department of Gastroenterology, Hahnemann Medical College, Philadelphia
NEUROLOGY AND PSYCHIATRY					
University of Illinois College of Medicine	Arranged on application	Seminars in psychiatry	Limited	Not available	Assistant to the Dean, University of Illinois College of Medicine, 1853 W. Polk St., Chicago
		8 lectures; 4 months in clinical child psychology	.....	Varies	
Harvard Medical School, Courses for Graduates	Nov. 10	6 days (injuries to brain and spinal cord)	15	$40 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Columbia University College of Physicians and Surgeons	October	Hours to be arranged in neuroanatomy, neuropathology, electroencephalography	Limited	$15 to $100	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	October	1 month or longer, afternoons (clinical neurology)	6	$50	
Graduate School of Medicine, University of Pennsylvania	Arranged on application [5]	10 weeks	.....	$100	Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia
	Arranged on application	8 weeks (clinical psychiatry)	.....	$160	
OBSTETRICS					
University of Chicago, The School of Medicine	Oct. 20	4 weeks, 10 times a year	7	$25	Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Ave., Chicago
University of Illinois College of Medicine	Sept. 29 and every 2 weeks	2 weeks (including pediatrics)	4	$10 [3]	Assistant to the Dean, University of Illinois College of Medicine, 1853 W. Polk St., Chicago
	Arranged on application	Obstetrics and gynecology in preparation for Board examinations	Limited	Varies	
Indiana University Medical Center	Nov. 3; Jan. 12	2 weeks	6	$10 [3]	Dr. Carl P. Huber, Coleman Hospital, Indiana University School of Medicine, Indianapolis
State University of Iowa College of Medicine	Oct. 6 and every 2 weeks	6 days	4	None	Associate in Obstetrics and Gynecology, University Hospitals, Iowa City
Louisiana State University School of Medicine	Quarterly	2 weeks	.....	$75 [3]	Supervisor, Maternal and Child Health Services, Department of Health, Civil Courts Bldg., New Orleans
Harvard Medical School, Courses for Graduates	Arranged on application	1 or more months (clinical; 1 month (pathology)	Limited; 2	$125 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
University of Michigan Medical School	Sept. 22 and every 2 weeks	2 weeks	4	None	Director, Bureau of Maternal and Child Health, Michigan Department of Health, Lansing
University of Nebraska School of Medicine	Every other week	2 weeks (including pediatrics)	.....	$10	Director of Maternal and Child Health, State Department of Health, Lincoln
Margaret Hague Maternity Hospital, Jersey City (Columbia University Coll. of P. and S.)	First of every month	1 to 3 months full time	24	$100 to $350	Medical Director, Margaret Hague Maternity Hospital, 88 Clifton Pl., Jersey City
New York Polyclinic Medical School and Hospital	October	2 months full time	.....	$250	Medical Executive Officer; New York Polyclinic Medical School, 335 W. 50th St., New York City

References will be found on page 1208.

Continuation Courses for Practicing Physicians, Fall of 1941—Continued

Institution	Courses Scheduled to Begin	Length and Content of Course	Number of Students Accepted for Each Course	Registration Fee and/or Tuition	For Detailed Information Write to
OBSTETRICS—Continued					
Duke Hospital, Durham	Every week	5 days (including pediatrics)	.....	None	Assistant State Health Officer, State Board of Health, Raleigh
University of Oklahoma School of Medicine	Arranged on application	15 days	6	$25	Dr. Edward N. Smith, Associate Professor of Obstetrics, 800 N.E. 13th St., Oklahoma City
University of Oregon School of Medicine (Washington State Department of Health)	Fall	5 to 7 days (including pediatrics)	30	$15 to $25	Director, Washington State Department of Health, Smith Tower, Seattle
Woman's Medical College of Pennsylvania	Sept. 17	8 month course	2	$100 to $300	Dean, Woman's Medical College of Pennsylvania, Henry Ave. and Abbottsford Rd., Philadelphia
Medical College of the State of South Carolina	Every other week	2 weeks (including pediatrics)	4	$50 [3]	Dean, Medical College of the State of South Carolina, Charleston
OPHTHALMOLOGY					
George Washington University School of Medicine	Jan. 26	6 days (surgery, pathology, orthoptics)	25	$100	Professor of Ophthalmology, George Washington University, School of Medicine, 1335 H St., N.W., Washington, D. C.
American Academy of Ophthalmology and Otolaryngology, Chicago	Oct. 19	5 days (ophthalmology and otolaryngology)	.....	Not available	Secretary for Instruction, Ophthalmology or Otolaryngology, 107 S. 17th St., Omaha
Northwestern University Medical School	Sept. 1	8 months, mornings or full time	.....	$400	Professor of Ophthalmology, Northwestern University Medical School, 303 E. Chicago Ave., Chicago
University of Illinois College of Medicine	October	12 months, mornings	10	$75 a semester plus laboratory and clinic fees	Assistant to the Dean, University of Illinois College of Medicine, 1853 W. Polk St., Chicago
	1st or 2d semester	4 months (pathology of the eye)	.....	$75 plus cost of materials	
Harvard Medical School, Courses for Graduates	Jan. 5; on arrangement	3 weeks, mornings or 1 month, afternoons; 3 months daily (refraction)	Limited	$80; $300 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
	Oct. 13	10 weeks (fundamental sciences)	15 or more	$250 [1]	
Tufts Medical School, Postgraduate Division	Every month	3 mornings a week	Limited	$50 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston
Washington University School of Medicine	Oct. 1	8 months, full time	.....	$800	Registrar, Washington University School of Medicine, Scott and Euclid Ave., St. Louis
Columbia University College of Physicians and Surgeons	Oct. 27	2 afternoons a week, 6 weeks (ophthalmoscopy)	4 to 6	$20	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Oct. 27 [2]	4 successive courses of 5-6 days	35	$25 to $60 a course	
New York Eye and Ear Infirmary	Arranged on application	1 to 3 months (including otolaryngology)	.....	$40 to $110	Registrar, New York Eye and Ear Infirmary, 218 Second Avenue, New York City
New York Polyclinic Medical School and Hospital	Oct. 1, Jan. 2, on application	6 weeks to 9 months (including otolaryngology)	.....	$50 to $1,000	Medical Executive Officer, New York Polyclinic Medical School, 335 W. 50th St., New York City
New York University College of Medicine	Arranged on application	11 months	.....	$400	Assistant Dean, New York University College of Medicine, 477 First Ave., New York City
Graduate School of Medicine, University of Pennsylvania	Arranged on application	2 or 3 weeks (operations on cadaver)	.....	$100 to $270	Dean Graduate School of Medicine, University of Pennsylvania, Philadelphia
		8 weeks (histology and pathology)	.....	$200	
Post Graduate Medical Assembly of South Texas	Dec. 2	3 days (including otolaryngology)	.....	$10	President, Post Graduate Medical Assembly of South Texas, 229 Medical Arts Bldg., Houston
ORTHOPEDIC SURGERY					
Harvard Medical School, Courses for Graduates	Oct. 27; on arrangement	6 days (fractures); 1 month, mornings	.....	$75; $50 [1]	Assistant Dean, Harvard Medical School, 25 Shattuck St., Boston
Columbia University College of Physicians and Surgeons	Oct. 13; Oct. 20	4 weeks, 3 afternoons; 6 days, full time	4 to 20	$35 to $50	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
	Jan. 19	9 days	5 to 20	$75 [3]	
New York Polyclinic Medical School and Hospital	Arranged on application	3 months	.....	$75 to $100	Medical Executive Officer, New York Polyclinic Medical School, 335 W. 50th St., New York City
OTOLARYNGOLOGY					
University of Illinois College of Medicine	Jan. 19	8 to 12 months	.....	$75 a semester	Assistant to the Dean, University of Illinois College of Medicine, 1853 W. Polk St., Chicago
Washington University School of Medicine	Sept. 22	8 months	.....	$600	Registrar, Washington University School of Medicine, Scott and Euclid Ave., St. Louis
Columbia University College of Physicians and Surgeons	Arranged on application [2]	3 weeks (bronchoscopy)	.....	$250	Dean of the School of Medicine, Columbia University, 630 W. 168th St., New York City
Tufts Medical School, Postgraduate Division	Any month	1 month, mornings	.....	$50 [1]	Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston

A limited number of opportunities for postgraduate study in the clinical departments are also offered by the University of Chicago, The School of Medicine; Tulane University of Louisiana School of Medicine; Johns Hopkins University School of Medicine; Duke University School of Medicine; Vanderbilt University School of Medicine; Meharry Medical College, and the University of Wisconsin Medical School.

1. Registration fee of $5 covers all courses taken within twelve months.
2. Admission is limited to physicians who have had adequate previous training and experience in the special field.
3. State boards of health furnish either the funds covering tuition fees, maintenance or transportation for physicians of the state.
4. Applicants may qualify for a monthly stipend from the United States Public Health Service.
5. A faculty course given for staff members of mental institutions.

(To be continued)

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

Chicago, Feb. 16-17, 1942. Council on Medical Education and Hospitals, Sec., Dr. William D. Cutter, 535 N. Dearborn Street, Chicago.

MEDICAL CORPS, UNITED STATES NAVY

Examination. Assistant Surgeon with the permanent rank of Lieutenant (junior grade), Oct. 6-9, and Jan. 5-9. Acting Assistant Surgeon with the probationary rank of Lieutenant (junior grade), Jan. 5-9. Examination will be held at the Naval Hospitals at Chelsea, Mass., Newport, R. I., Brooklyn, Philadelphia, Norfolk, Va., Charleston, S. C., Pensacola, Fla., Corpus Christi, Tex., San Diego and Mare Island, Calif., Puget Sound, Wash., Great Lakes, Ill., Pearl Harbor, T. H., and Naval Medical Center, Washington, D. C. Apply Rear Admiral Ross T. McIntire, M.D., Surgeon General, U. S. Navy, Washington, D. C.

BOARDS OF MEDICAL EXAMINERS
BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examinations of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, September 27, page 1115.

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Part III. Baltimore and New York City, October; Boston, November. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: *Oral.* Dec. 12-13. Final date for filing application is Nov. 8. Sec., Dr. C. Guy Lane, 416 Marlboro St., Boston.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* April, in advance of the meeting of the American College of Physicians and June, in advance of the meeting of the American Medical Association. Applications should be on file 6 weeks in advance of the date of oral examination. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written. Part I. Group B.* Various centers. Jan. 3. *Oral. Part II. Groups A and B.* Atlantic City, May or June. Final date for filing application is March 1. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* March 7. Final date for filing application is Dec. 1. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: Washington, January. Final date for filing application is Nov. 1. Sec., Dr. Guy A. Caldwell, 3503 Prytania St., New Orleans, La.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral and Written. All Groups.* Philadelphia, June, preceding the meeting of the American Medical Association. Final date for filing application is March 1. Sec., Dr. W. P. Wherry, 1500 Medical Arts Bldg., Omaha, Neb.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Philadelphia, March or April, at the time of the Region I meeting of the American Academy of Pediatrics. Cleveland, May, at the time of the Region III meeting of the American Academy of Pediatrics. Los Angeles, May, at the time of the Region IV meeting of the American Academy of Pediatrics. *Written.* Locally in approximately 6 weeks in advance of the date of oral examination. Sec., Dr. C. A. Aldrich, 707 Fullerton Ave., Chicago.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral.* New York, Dec. 19-20. Final date for filing application is Oct. 5. Sec., Dr. Walter Freeman, 2023 Connecticut Ave., N.W., Washington, D. C.

AMERICAN BOARD OF RADIOLOGY: *Oral. All Groups.* Atlantic City, June 4. Final date for filing application is April 1. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S. W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written. Part I.* Various centers, Oct. 6. *Oral. Part II.* New York Nov. 10-11. A meeting of the board will follow on the 12th. Sec., Dr. J. Stewart Rodman, 225 S. Fifteenth St., Philadelphia.

AMERICAN BOARD OF UROLOGY: *Written.* Various centers, December. *Oral.* Chicago, February. Final date for filing application is Nov. 1. Sec., Dr. Gilbert J. Thomas, 1009 Nicollet Ave., Minneapolis.

Illinois January Report

The Illinois Department of Registration and Education reports the written examination (graduates of foreign schools given also a practical test) for medical licensure held at Chicago, Jan. 21-23, 1941. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Eighty-one candidates were examined, 61 of whom passed and 20 failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Howard University College of Medicine		(1939)	80
Chicago Medical School	77, 77, 80, 81, 86,	(1941)	80
Loyola University School of Medicine	81, 81,	(1940)	78,
Northwestern University Medical School	76, 86, 86, 88	(1938)	75,
Rush Medical College	77, 80, 82,* 82, 83, 84, 85	(1937)	84,
University of Chicago, The School of Medicine	(1939) 79, 81, 84, 85, 86*	(1936)	86,
University of Illinois College of Medicine	(1939) 80,* (1940) 78,* 78, 83,* 83, 84, 84,	(1941)	81 78,
Harvard Medical School		(1938)	80
Washington University School of Medicine		(1924)	79, (1938) 82
University and Bellevue Hospital Medical College		(1913)	75
University of Oregon Medical School		(1937)	83*
Medizinische Fakultät der Universität Wien	(1909) 76, (1923) 76	(1900)	78,
Deutsche Universität Medizinische Fakultät, Prag	(1938) 79	(1911)	75,
Universita Karlova Faculta Lékařská, Praha		(1932)	79
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin		(1933)	75
Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main		(1934)	77
Medizinische Akademie Düsseldorf		(1928)	81
Universität Heidelberg Medizinische Fakultät		(1933)	76
Magyar Királyi Pázmány Péter Tudományegyetem Orvosi Fakultasa, Budapest		(1921)	76
Universität Basel Medizinische Fakultät		(1939)	77

School	FAILED	Year Grad.	Number Failed
University of Illinois College of Medicine		(1940, 2)	2
Medizinische Fakultät der Universität Wien		(1920), (1935), (1936), (1937)	4
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin		(1921), (1923, 2)	3
Hamburgische Universität Medizinische Fakultät		(1922)	1
Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main		(1921)	1
Julius-Maximilians-Universität Medizinische Fakultät, Würzburg		(1909), (1915)	2
National University of Athens School of Medicine		(1939)	1
Magyar Királyi Erzsébet Tudományegyetem Orvostudományi, Pecs		(1923), (1933)	2
Universidad Libre Mexicana Instituto de Ciencias		(1929)	1
Universiteit van Amsterdam Geneeskunde Faculteit		(1934)	1
Universität Basel Medizinische Fakultät		(1939)	1
Université de Lausanne Faculté de Médecine		(1939)	1

Twenty-one physicians were successful in the practical test for reciprocity and endorsement applicants held in Chicago, January 23. The following schools were represented:

School	PASSED	Year Grad.	Reciprocity with
Stanford University School of Medicine		(1933)	California
Rush Medical College		(1923),* (1937)*	Utah
Indiana University School of Medicine		(1931)	Indiana
Johns Hopkins University School of Medicine		(1939)	Maryland
University of Michigan Medical School		(1927),* (1938)	Michigan
Washington University School of Medicine		(1939, 2)	Missouri
Creighton University School of Medicine		(1939)*	Nebraska
Ohio State University College of Medicine		(1939)	Ohio
Temple University School of Medicine		(1937)	Penna.
University of Tennessee College of Medicine		(1930)	Maryland
University of Toronto Faculty of Medicine	(1924),* (1937)* Ohio	(1922)	Michigan,

School	PASSED	Year Grad.	Endorsement of
Rush Medical College		(1938),* (1939)	N. B. M. Ex.
The School of Medicine of the Division of the Biological Sciences		(1938)*	N.B.M.Ex.
Boston University School of Medicine		(1938)	N. B. M. Ex.
Albany Medical College		(1939)	N. B. M. Ex.

* Licenses have not been issued.

Nebraska June Report

The Bureau of Examining Boards of the State of Nebraska reports the written examination for medical licensure held at Omaha, June 12, 1941. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Ninety-one candidates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Creighton University School of Medicine	82.3, 82.5, 82.7, 83.4, 83.9, (1941) 80.3, 81.5, 82.2, 82.7, 83.6, 83.7, 83.8, 84, 84.3, 85.2, 85.5, 85.9, 86.1, 86.9, 88.1	(1940)	78.8,
University of Nebraska College of Medicine	(1937) 82.8, (1940) 79.2, 83.8, (1941) 77.5, 77.7, 78, 79.3, 79.3, 79.5, 80.5, 80.5, 80.6, 80.8, 80.8, 81.1, 82, 82, 82.2, 82.3, 82.3, 82.3, 82.5, 82.7, 82.8, 82.9, 83.2, 83.2, 83.2, 83.3, 83.3, 83.4, 83.6, 84, 84, 84.1, 84.3, 84.3, 84.3, 84.4, 84.5, 84.7, 84.8, 84.8, 84.9, 85.1, 85.2, 85.2, 85.3, 85.4, 85.9, 86, 86.3, 86.3, 86.5, 86.5, 86.6, 87, 87.3, 87.6, 87.6, 87.7, 87.7, 87.9, 88, 88.3, 88.7, 90.9, 91, 91.7	(1935)	81.1,

Alabama June Report

The Alabama State Board of Medical Examiners reports the written examination for medical licensure held at Montgomery, June 17-19, 1941. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Twenty-eight candidates were examined, 25 of whom passed and 3 failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
George Washington University School of Medicine		(1940)	79.1
Howard University College of Medicine		(1939)	75.3
Emory University School of Medicine	(1940) 90.1,* (1941) 87.6*	(1939)	82.9,
Northwestern University Medical School		(1941)	86.2*
Rush Medical College		(1940)	83.1

University of Louisville School of Medicine.....(1941)* 81.3, 85.2
Tulane University of Louisiana School of Medicine....(1941)* 86.4, 87, 87.1, 87.4, 87.9, 88, 89.7, 89.7, 91.6
Washington University School of Medicine.....(1941) 90.8*
Jefferson Medical College of Philadelphia.....(1941) 84*
University of Pennsylvania School of Medicine.....(1941)* 86.2, 89.2
Woman's Medical College of Pennsylvania.....(1941) 85.8*
University of Tennessee College of Medicine.....(1941)* 83.6, 83.9

School	FAILED	Year Grad.
Birmingham Medical College		(1914)
Boston University School of Medicine		(1923)
University of Nashville Medical Department		(1907)

* Licenses have not been issued.

Missouri Reciprocity Report

The State Board of Health of Missouri reports 8 physicians licensed to practice medicine by reciprocity and 1 physician so licensed on endorsement of credentials of the National Board of Medical Examiners on May 28. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
University of Arkansas School of Medicine		(1940)	Arkansas
Northwestern University Medical School		(1938)	Michigan
University of Kansas School of Medicine		(1939), (1940)	Kansas
University of Louisville Medical Department		(1916)	Wyoming
University of Maryland School of Medicine and College of Physicians and Surgeons		(1919)	Maryland
University of Tennessee College of Medicine		(1940)	Tennessee
Licentiate of the Royal College of Physicians, of the Royal College of Surgeons of Edinburgh and of the Royal Faculty of Physicians and Surgeons, Glasgow		(1939)	New York

School	LICENSED BY ENDORSEMENT	Year Grad.
Meharry Medical College		(1936)

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Hospitals: Liability for Failure to Place Side Rails on Patient's Bed.—Edgar Pennington, aged 21, was admitted as a pay patient to the defendant hospital suffering from an unstated malady which apparently called for restraint and isolation. When first admitted, side rails were placed on his bed, but they were subsequently removed and his left leg was chained to the bed. A few weeks later he was found lying with his head on the concrete floor of his room, apparently unconscious and "in a bloody condition." He was given prompt medical attention and side rails were immediately reinstalled on his bed. He died three days after the mishap. It was then ascertained that his skull "had been severely fractured and that this fracture was of such a serious nature as to cause death." The patient's father and mother brought suit against the hospital, alleging that death resulted from injuries occasioned by the fall from the bed while the patient was irrational and that the fall, in turn, was the result of the negligent failure of the hospital to take necessary precautionary methods by installing guard rails on the bed and to keep attendants on duty to prevent the patient from injuring himself. At the close of the plaintiff's evidence the trial court sustained a demurrer to the evidence and directed a verdict in favor of the hospital. Thereafter, apparently believing that it had erred in so doing, the trial court sustained a motion for a new trial made by the plaintiffs and the hospital appealed to the Supreme Court of Oklahoma.

The principal question for the determination of the Supreme Court was whether or not the evidence adduced by the plaintiffs at the trial was sufficient to make out a prima facie case of negligence against the hospital. If it did, the trial court was in error in directing a verdict for the hospital but was correct in granting a new trial after doing so. The Supreme Court believed that the evidence adduced by the plaintiffs was sufficient to make out a prima facie case against the hospital. In a civil action, said the Supreme Court, the plaintiff is not required to prove his case beyond a reasonable doubt. All that he must prove are facts making it appear more probable that the injury resulted in whole, or in part, from the defendant's negligence than from any other cause. This may be done by circumstantial evidence and the reasonable inferences to be drawn therefrom. The fact that Pennington was placed in the hospital, side rails were kept on his bed for the first few days and thereafter his leg was chained to the bed is sufficient to justify a reasonable inference that the hospital authorities knew that his condition was such that restraint was necessary. The question of whether the proper method was adopted for such restraint or protection was for the jury. The fact that after his alleged fall side rails were again installed would be some evidence that the chaining of the patient's leg was not of itself a sufficient method of restraint. While no one testified directly that the alleged fall from the bed caused the skull injuries, the fact that thereafter the boy's head was bandaged, that he never talked thereafter and that his body, when examined, was in the same condition as when removed from the hospital is sufficient to justify a reasonable inference that such injuries resulted from the fall. Likewise, while the evidence does not establish that Pennington's death was the result of the skull fracture, the fact that he never spoke after the mishap, that he died on the third day following and that the injury to the head was such that death would probably result therefrom justifies a presumption that death was caused thereby. From the circumstances proved by the plaintiffs, coupled with the circumstantial evidence that Pennington's death resulted from a fall from the bed, the jury might reasonably infer that death resulted from the head injuries, and such an inference would not be based wholly on the inference that the injuries resulted from the fall. It would also be based on the facts and circumstances surrounding the death. As this court said in *Gypsy Oil Co.* v. *Ginn*, 152 Okla. 30, 3 P. (2d) 714:

> A guess cannot be based on a guess, nor a guess on an inference, nor an inference on a guess, but an inference may be based upon an inference, if the inference is a justifiable conclusion based upon competent evidence, either direct or circumstantial.

For the reasons stated, the Supreme Court concluded that the trial court was warranted in awarding a new trial and accordingly affirmed the judgment of the lower court to that end. —*Morningside Hospital & Training School for Nurses v. Pennington et al., 114 P. (2d) 943 (Okla., 1941).*

Society Proceedings

COMING MEETINGS

American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 19-23. Dr. William P. Wherry, 107 South 17th St., Omaha, Executive Secretary.
American Academy of Pediatrics, Boston, Oct. 8-11. Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill., Secretary.
American Clinical and Climatological Association, Skytop, Pa., Oct. 16-18. Dr. Francis M. Rackemann, 263 Beacon St., Boston, Secretary.
American College of Surgeons, Boston, Nov. 3-7. Dr. Frederic A. Besley, 40 East Erie St., Chicago, Secretary.
American Public Health Association, Atlantic City, N. J., Oct. 14-17. Dr. Reginald M. Atwater, 50 West 50th St., New York, Executive Secretary.
American Society of Tropical Medicine, St. Louis, Nov. 11-14. Dr. E. Harold Hinman, Wilson Dam, Ala., Secretary.
Associated Anesthetists of the United States and Canada, Boston, Nov. 3-7. Dr. C. J. Wells, 1932 S. Salina St., Syracuse, N. Y., Secretary.
Association of Military Surgeons of the United States, Louisville, Ky., Oct. 29-Nov. 1. Colonel James M. Phalen, Army Medical Museum, Washington, D. C., Secretary.
Central Society for Clinical Research, Chicago, Nov. 7-8. Dr. Carl V. Moore, Washington University School of Medicine, St. Louis, Secretary.
Delaware, Medical Society of, Wilmington, Oct. 7-8. Dr. C. L. Munson, 1015 Washington St., Wilmington, Secretary.
Inter-State Postgraduate Medical Association of North America, Minneapolis, Oct. 13-17. Dr. Tom B. Throckmorton, 406 Sixth Ave., Des Moines, Iowa, Secretary.
Omaha Mid-West Clinical Society, Omaha, Oct. 27-31. Dr. J. D. McCarthy, 1036 Medical Arts Bldg., Omaha, Secretary.
Pennsylvania, Medical Society of the State of, Pittsburgh, Oct. 6-9. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh, Secretary.
Southern Medical Association, St. Louis, Nov. 10-13. Mr. C. P. Loranz, Empire Bldg., Birmingham, Ala., Secretary.
Virginia, Medical Society of, Virginia Beach, Oct. 6-8. Miss A. V. Edwards, 1200 East Clay St., Richmond, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1931 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Diseases of Children, Chicago

62:1-230 (July) 1941

Hereditary Factors in Blood Dyscrasias. T. B. Cooley, Detroit.—p. 1.
*Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids: Based on Study of 186 Allergic Children. M. M. Peshkin, New York.—p. 9.
Electrocardiographic Alterations in Rheumatic Fever in Children. E. S. Orgain, J. M. Martin, Durham, N. C., and H. I. G. Anderson, Memphis, Tenn.—p. 26.
Developmental Pattern of Child as Reflected in Calcification Pattern of Teeth. M. Massler, I. Schour and H. G. Poncher, Chicago.—p. 33.
Extreme Eosinophilia and Leukocytosis: Unusual Clinical Syndrome of Unknown Origin Occurring in Childhood. M. H. Bass, New York.—p. 68.
Emotional Factor in Bronchial Asthma in Children. R. A. Jensen and A. V. Stoesser, Minneapolis.—p. 80.
Relation of Streptococcic Antifibrinolysin to Acute Rheumatic Fever. J. A. Lichty Jr., Rochester, N. Y.—p. 92.
*Follicular Conjunctivitis in School Children as Expression of Vitamin A Deficiency. Margaret R. Sandels, Helen Dorothy Cate, Kathleen Perry Wilkinson and L. J. Graves, Tallahassee, Fla.—p. 101.
Nonspecific Ulcerative Colitis in Childhood. J. Elitzak and A. H. Widerman, New York.—p. 115.
Further Evidence of Destruction of Thiamine in Evaporated Milk. Amy L. Daniels, Iowa City.—p. 127.
Medallions and Plaques of Interest to Pediatricians. A. Levinson, Chicago.—p. 159.

Immunity to Tetanus.—Peshkin determined the minimal number of doses of alum-precipitated diphtheria and tetanus toxoids required to immunize 186 children suffering from hay fever, asthma or allergic rhinitis against tetanus. Their ages ranged from 3 to 15 years. The combined preparation was injected subcutaneously in two doses of 0.5 cc. each at intervals of from one to ten months. With few exceptions the patients were also treated with pollens and other antigens during the period of observation. Local harmless reactions occurred after the first and second injections in about 25 per cent of the children. No general constitutional reaction (urticaria or asthma) occurred. Of the 186 children, 176 had protective levels (not less than 0.1 American unit of antitoxin per cubic centimeter of blood) of tetanus antitoxin following the two doses. Nine of the 10 children with inadequate antitoxin levels were given a third or "stimulating" dose of combined alum-precipitated toxoids, and within one month all had adequate antitoxin levels. The children of preschool age acquired adequate immunity to tetanus after the two doses of the combined toxoids were injected at intervals of from one to ten months, whereas the protection in children of school age was acquired only after receiving injections at intervals of from five to ten months. The initial maximal antitoxin level was reached by almost all children in from seven to thirty days after they had received the toxoids. All of the 176 children maintained adequate antitoxin levels for three months after receiving the toxoids, in one year 65.4 per cent had adequate antitoxin titers and after two years 43 per cent had protective levels. Of the 176 children, 139 were given the injections at intervals of from one to four months and 37 at intervals of from five to ten months. A significantly greater percentage of the latter group responded by the highest antitoxin values not only within one hundred days of receiving the two doses but one year after the immunization. Thus the interval between the two doses had a direct influence on antitoxin response. In the absence of any practical test to determine immunity, adequate active protection against tetanus might be assured for all children by three doses (of 0.5 cc. each) of alum-precipitated toxoid administered at intervals of not less than one month. At the time of injury a "stimulating" dose of alum-precipitated tetanus toxoid could be given. If exposure to tetanus occurs before vaccination is completed and immunity is established, a simultaneous injection of antitetanus serum and toxoid (serovaccination) should be given.

Follicular Conjunctivitis.—Sandels and her co-workers studied the effect of supplementary vitamin A on the conjunctival folliculosis of 119 school children. Twenty-one of the 22 children who received supplementary vitamin A showed improvement; 11 of them were entirely free of follicular conjunctivitis at the end of nine weeks of observation. There was no improvement in 17 control children observed over the same period. All of the 60 children given graduated amounts of vitamin A were improved, and 40 were entirely free of the conjunctivitis in twelve weeks. Of 20 children who received no supplementary vitamin during a similar period, only the 2 who had received a more liberal diet showed any improvement. Children who received 13,000 U. S. P. units of vitamin A improved at approximately the same rate as did those who received 25,000 or 38,000 units. Apparently time is a factor limiting the rate of healing, and excessive doses of vitamin A do not increase this rate proportionately. A concentrate of vitamin A esters containing a negligible amount of vitamin D produced as rapid improvement as did a concentrate containing vitamin D. A survey of the diets of 58 children, 42 of whom had follicular conjunctivitis and 16 who did not, shows that the deficiency developed with a diet having a vitamin A content of less than 100 U. S. P. units per kilogram of body weight daily. The survey suggests that diets in which carotene furnishes a large proportion of the vitamin A value from 200 to 250 U. S. P. units of vitamin A per kilogram of body weight a day will not provide a too generous allowance for children between 6 and 12 years of age. The presence or absence of follicular conjunctivitis as an indication of vitamin A nutrition is a more reliable measure for children from 6 to 12 years of age than it is for older boys and girls.

American Journal of Hygiene, Baltimore

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Reliability of Certificates of Deaths from Cancer. H. F. Dorn and J. I. Horn, Washington, D. C.—p. 12.
Diphtheria Immunization, Natural and Artificial, in Eastern Health District of Baltimore, 1922-1940. C. H. Eller and J. J. Phair, Baltimore.—p. 28.

Section B

Experimental Air-Borne Disease: Quantitative Natural Respiratory Contagion of Tuberculosis. W. F. Wells and M. B. Lurie, Philadelphia.—p. 21.

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Arkansas Medical Society Journal, Fort Smith

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Pneumococcic Meningitis with Recovery. S. J. Wolfermann and L. A. Whittaker, Fort Smith.—p. 44.

Florida Medical Association Journal, Jacksonville

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Georgia Medical Association Journal, Atlanta

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Intravenous Cholecystography: Review of 500 Cases. A. A. Rayle and W. P. Elkin, Atlanta.—p. 228.
Sarcoma of Breast. E. L. Bishop, Atlanta.—p. 232.
Differential Diagnosis of Jaundice and Carotenemia: Report of Case. R. H. Wood and E. B. Agnor, Atlanta.—p. 239.

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Georgia's Medical Problems of Today. J. C. Patterson, Cuthbert.—p. 257.
Presentation of Gold Key to Retiring President, Dr. J. C. Patterson. S. P. Kenyon, Dawson.—p. 260.
Bronchography in Chest Diseases. S. C. Lynn, Savannah.—p. 262.
Duodenal Ulcer in Children: Report of Case. T. I. Willingham, Atlanta.—p. 271.
Rocky Mountain Spotted Fever in Sumter County: Report of Case. J. C. Logan, Plains.—p. 274.
Paroxysmal Hemoglobinuria: Report of Case. R. B. Logue, Atlanta.—p. 275.

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Congenital Anomaly: Rotation of Kidney. G. D. Oppenheimer and B. S. Wolf, New York.—p. 17.
Renal Pain: Symptom in Acute Cystitis. R. L. Dourmashkin and A. A. Solomon, New York.—p. 28.
Hypothyroidism and Bladder Function: Experimental Study. J. W. Sherrill and E. M. Mackay, La Jolla, Calif.—p. 34.
Carcinoma of Urinary Bladder Imitating Sarcoma. J. R. McDonald, A. K. Doss and G. J. Thompson, Rochester, Minn.—p. 38.
*Endometriosis of Urinary Bladder: Report of Two Additional Cases. P. J. Kahle, G. W. Vickery and E. Maltry, New Orleans.—p. 52.
Longevity Following Ureterointestinal Anastomosis: Report of Cases. R. Stevens, New York.—p. 57.
Treatment of Epididymitis by Infiltration of Spermatic Cord with Procaine Hydrochloride. D. R. Smith, San Francisco.—p. 74.
Patent Urachus with Stone Formation. M. L. Dreyfuss and M. M. Fliess, Clifton Forge, Va.—p. 77.
Etiology and Prevention of Oxalate Calculi in Urinary Tract: Plan of Therapy. C. E. Burkland, Baltimore.—p. 82.
*Treatment of Gonorrheal Urethritis in Male with Sulfadiazine: Analysis of Fifty-Seven Cases. L. W. LaTowsky, R. B. Baker, F. Knight and C. A. W. Uhle, Philadelphia.—p. 89.
*Antibacterial Activity of Sulfadiazine Toward Bacillus Coli and Enterococci Isolated from Patients with Infections of Urinary Tract. E. Neter, Buffalo.—p. 95.
Use of Sulfadiazine in Urinary Tract Infections and Gonorrhea and as Prophylactic to Prevent Postoperative Infections. R. W. Satterthwaite, Justina H. Hill and H. H. Young, Baltimore.—p. 101.
Effect of Hypophysectomy on Morphologic Appearance of Kidney and on Renotropic Action of Steroid Hormones. H. Selye, Montreal, Canada.—p. 110.
Chemical Composition of Prostatic Secretion in Relation to Benign Hypertrophy of Prostate. R. A. Moore, St. Louis; Mary L. Miller, and A. McLellan, New York.—p. 132.
Metabolism of Surviving Prostatic Tissue in Relation to Benign Hypertrophy of Prostate. S. Tollins, Brooklyn, and R. A. Moore, St. Louis.—p. 138.
New Technic for Intravenous Urography. W. A. H. Councill, Baltimore.—p. 143.

Endometriosis of Urinary Bladder.—Kahle and his co-workers report the forty-third and forty-fourth cases of endometriosis of the bladder. In their first case the mucosa was not involved, hematuria was not present and endometrial infiltration was discovered during the gynecologic operation for uterine fibroids. Consequently the vesical involvement was not suspected before operation and cystoscopy was not carried out. This instance is 1 of the few recorded cases in which pelvic surgery did not precede the development of the endometriosis of the bladder. In their other patient who had had previous gynecologic surgery, the vesical mucosa was involved and for six years hematuria was present at intervals. This case is unusual in that a vesicosigmoid fistula developed, though it is not possible to say whether it followed the apparently superficial injury of the sigmoid at the first operation or whether it was the result of the endometrial process.

Gonorrheal Urethritis and Sulfadiazine.—LaTowsky and his associates used sulfadiazine for treating 57 men with gonorrheal urethritis. Two of the men defaulted, and of the remaining 55 who were followed 51 were cured after an average of eight days of treatment. The total dose of the drug required to effect a cure ranged from 4 to 58 Gm.; the average was 17.5 Gm. The criteria of cure included as the final provocative test two or more negative smears and cultures of prostatic fluid. The time elapsing between the beginning of sulfadiazine therapy and the cessation of discharge in the cured patients averaged four days and ranged from one to thirty days. The time elapsing between sulfadiazine treatment and the first negative culture of the prostatic fluid averaged thirteen days; it ranged from three to forty-three days. The interval between the disappearance of the symptoms of gonorrheal urethritis to the last positive culture averaged three days and ranged from zero to eighteen days. The only symptom of toxicity following sulfadiazine therapy was headache in 5 men, a total incidence of 8.8 per cent.

Antibacterial Activity of Sulfadiazine.—Neter determined the in vitro bacteriostatic and bactericidal activity of sulfadiazine toward Escherichia coli and enterococci that were isolated in the urine from patients with infections of the urinary tract. Sulfadiazine exerted bacteriostatic activity in culture mediums by delaying and partly inhibiting the growth of E. coli. All strains of E. coli tested thus far were susceptible to its action. Compared to other sulfanilamide drugs, sulfadiazine in a concentration of 100 mg. per hundred cubic centimeters was definitely less effective than equal concentrations of sulfathiazole, somewhat more effective than sulfanilamide and sulfanilylguanidine and about as effective as sulfapyridine. Another experiment carried out to determine the bacteriostatic and bactericidal acivity of sulfadiazine on E. coli suspended in normal human urine showed that sulfadiazine in a concentration of 100 mg. per hundred cubic centimeters completely prevented visible growth of E. coli in urine for twelve days. It also exerted a definite bacteriostatic activity in highly diluted broth. In contrast the drug showed only negligible bacteriostatic activity in slightly diluted broth. Sulfadiazine caused loss of viability of the organisms in urine after four days of incubation, whereas it failed to kill them in buffer solution even after a lapse of twelve days. No bactericidal activity was demonstrable in slightly diluted broth, but it caused loss of viability in highly diluted broth. The following treatment of a patient with pyelitis due to E. coli suggests that sulfadiazine may be of value in treating such infections. Sulfanilamide failed to eradicate the infection, although its free concentration in the urine varied between 196 and 328 mg. per hundred cubic centimeters and therapy was continued for twelve days. Sulfadiazine given subsequently sterilized the urine and cured the patient within a few days. The concentration of sulfadiazine in the urine varied between 169 and 226 mg. per hundred cubic centimeters. In thirty-six experiments with six different strains of hemolytic and nonhemolytic enterococci sulfadiazine, in a concentration of 100 mg. per hundred cubic centimeters, exerted bacteriostatic activity in thirty instances.

Military Surgeon, Washington, D. C.

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North Carolina Medical Journal, Winston-Salem

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Radiology, Syracuse, N. Y.

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Late Results in Benign Giant Cell Tumor of Bone Obtained by Radiation Therapy. T. Leucutia, E. R. Witwer and G. Belanger, Detroit. —p. 1.
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*Roentgenologic Manifestations of Pulmonary Edema. C. B. Nessa and L. G. Rigler, Minneapolis.—p. 35.
*Compression of Heart. C. S. Beck, Cleveland.—p. 47.
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Effect of High and Low Body Temperatures on Growth of Irradiated Mouse Sarcoma 180. K. Sugiura, New York.—p. 85.
Effect of Shockproof Cables and Condensers on Two Valve Half Wave Rectification. M. M. D. Williams, Rochester, Minn.—p. 94.

Pulmonary Edema.—Nessa and Rigler found numerous variations from the classic roentgen appearance of pulmonary edema. Some of the variations from the typical butterfly-shaped, fairly symmetrical density simulate other pulmonary lesions to such a degree that frequent diagnostic errors result. The authors compared the roentgenogram against the postmortem observations of 17 cases among the 110 moderate to severe instances of pulmonary edema. The median age for the group was 57 years; the range was between 3 months and 80 years. In the 17 instances of which satisfactory roentgenograms had been obtained during life there was a close approximation between the extent and localization of the edema as shown on the roentgenogram and that seen at postmortem examination. The irregular distribution of density, the tendency toward localized accumulation of fluid and the lack of homogeneity in the shadows tended toward errors in diagnosis; e. g., pulmonary congestion, pneumonia, pneumococcic infarct, pneumoconiosis, atelectasis and bronchopneumonia. The possibility that some of the localized lesions may represent massive atelectasis has been suggested. However, none of the collateral signs of atelectasis—displacement of the mediastinum, elevation of the diaphragm or collapse of the ribs—are present. The absence of atelectasis was confirmed at necropsy. The differentiation from pneumonic consolidation or pulmonary infarct is difficult. The tendency for edema to give a clearer periphery is of some value. In any patient with roentgen signs of consolidation the presence of some adequate cause for pulmonary edema should dictate caution in the diagnosis of pneumonia or infarct. A definite differential diagnosis is impossible in atypical cases. In many patients with extensive pulmonary edema the physical changes are minimal. This discrepancy may be explained by the shallow breathing of such persons which makes physical signs difficult to obtain and by the fact that the tendency for the fluid to accumulate deeply in the lung rather than at the periphery may reduce the transmission of abnormal sounds. Pulmonary edema was usually found to be more severe in the right than in the left lung, but in some instances the reverse was true. Pulmonary edema should be considered in cases of cardiac failure, renal disease, hepatic disease, after operations and following transfusion reactions.

Compression of Heart.—Beck divides diseases of the heart into intrinsic and extrinsic cardiac lesions; that is, cardiac lesions and hearts crippled by some factor outside the heart. In extrinsic lesions if the outside factor can be removed by operation the patient can be cured. Extrinsic lesions consist of angulation, rotation and compression. Angulation or rotation when applied to a heart experimentally produces tachycardia, a fall in arterial pressure and a rise in venous pressure. Compression of the heart may be acute or chronic. Acute compression is produced by a fluid pressure on the outside of the heart. A gas may compress the heart if it collects under pressure, as in pressure pneumothorax. The author's diagnostic triad for acute compression consists of a rising venous pressure, a falling arterial pressure and a small quiet heart. An acute compression of about 20 cm. of water is usually fatal. The venous pressure goes up to about the same pressure as that exerted on the heart. The compression reaches a fatal level when the venous pressure cannot equalize the pressure on the heart. The height to which the venous pressure can rise determines the prognosis, life or death. Venous pressure can be raised by intravenous blood and dextrose or sodium chloride solution. This may be used to keep the patient alive while preparation is being made for operation. In chronic compression the venous pressure can rise much higher than in the acute condition. The rise is a protection against compression and, if reduced by blood letting, the patient dies. In chronic compression the arterial pressure does not fall as it does in acute compression. The compressed heart cannot dilate or hypertrophy. The heart is always small and atrophic because of disuse. The circulating blood volume increases and the amount of blood put out by the heart per unit of time is reduced. The heart plays a passive part. As long as six months may be necessary after the compression has been removed by operation for the disuse atrophy to be overcome. Another manifestation of chronic compression is water logging. The heart itself is a quiet organ. There are no murmurs because the disease is extrinsic, and the intrinsic cardiac structures are not involved. After the clinical diagnosis is made the anatomic lesion producing the compression must be determined. The lesions capable of producing chronic cardiac compression are pericardial compression scars (not adhesions), blood, pus, transudate or exudate in the pericardial cavity or mediastinal space, tumors of the heart or pericardium, strangulation of the heart through a rent in the pericardium and several other rare conditions. Chronic pulmonary fibrosis is the only condition that may simulate chronic cardiac compression. Nothing need be done about the adhesions that may form between the heart, the wall of the chest and the diaphragm after the compression scar has been removed. Surgery of compression scars is dramatic and scarcely less than miraculous in its immediate and remote effects on the patients who can be cured. They can be converted permanently from chronic cardiac invalids into healthy persons. There is no other treatment except surgical intervention.

Rhode Island Medical Journal, Providence

24:125-144 (July) 1941

Benjamin Waterhouse. H. G. Partridge, Providence.—p. 125.
Lung Involvement Secondary to Infections of Upper Respiratory Tract, L. E. Burns, Newport.—p. 127.
Measles. H. G. Calder, Providence.—p. 129.
Immunization Against Diphtheria. E. F. Kelly, Pawtucket.—p. 129.
Maternal Mortality. J. G. Walsh, Providence.—p. 130.

Rocky Mountain Medical Journal, Denver

38:497-592 (July) 1941

Subtotal Gastrectomy. R. B. Hill, Denver.—p. 514.
Treatment of Fractures of Neck of Femur by Internal Fixation (Blind Nailing): Review of Thirty-Seven Cases. A. Thomas, C. E. Sevier and F. Matchett, Denver.—p. 518.
Treatment of Burns. R. T. Richards, Salt Lake City.—p. 521.
Some Practical Points in Treatment of Empyema. F. R. Harper, Denver.—p. 526.
Surgical Management of Anorectal Disease. M. C. Lindem, Salt Lake City.—p. 530.
Diagnosis and Treatment of Expanding Lesions of Cranial Cavity. W. R. Lipscomb, Denver.—p. 553.

Southern Medical Journal, Birmingham, Ala.

34:681-788 (July) 1941. **Partial Index**

The Great Physician. A. T. McCormack, Louisville, Ky.—p. 681.
Cesarean Section, with Special Reference to Lower Segment Operations: Analysis of 110 Consecutive Cases. W. R. Payne and H. G. Bland, Newport News, Va.—p. 689.
Treatment of Pruritus of Perineum, Labia and Vagina by Newer Methods, Including Injection of Alcohol and Use of Stilbestrol and Astringent Cresol Derivative. L. R. Wharton, Baltimore.—p. 694.
Easier and Safer Cataract Extraction. F. M. Cooper, Oklahoma City.—p. 698.
Review of Recent Research on Drug Prophylaxis and Treatment of Malaria. H. C. Clark, Panama, Republic of Panama.—p. 703.
Malaria Mortality in Southern United States for the Year 1939, with Notes on Malaria in Other States. E. C. Faust, New Orleans.—p. 708.
Studies on Induced Quartan Malaria in Negro Paretics: III. Measurements of Paroxysmal Phases. M. D. Young, G. R. Coatney and S. B. McLendon, Columbia, S. C.—p. 709.
Vascular Birthmarks. H. G. F. Edwards, Shreveport, La.—p. 717.
Gonadotropins: Clinical and Experimental Study. R. B. Greenblatt and E. R. Fund, Augusta, Ga.—p. 730.
Chronic Urinary Infections in Children. J. M. Pace, Dallas, Texas.—p. 745.
Rehabilitation of Cerebral Palsy. W. M. Phelps, Baltimore.—p. 770.
Fractures of Humerus Treated by Hanging Cast. R. A. Griswold, D. C. Hucherson and E. C. Strode, Louisville, Ky.—p. 777.

Surgery, St. Louis

10:1-206 (July) 1941

Role of Epithelization and Contracture in Healing of Peptic Ulcer: Preliminary Report. E. L. Howes, S. C. Bullock and B. Syphax, Washington, D. C.—p. 1.
Autogenous Cartilage Grafts: Experimental Study. F. Young, Rochester, N. Y.—p. 7.
Studies of Jugular Pressure of Anesthetized Dogs During Positive Inflation of Lungs Before and After Pneumonectomy. G. H. Humphreys, R. L. Moore and H. Barkley, New York.—p. 21.
Observations on Use of Prolonged Anesthetic Agents in Upper Abdominal Incisions. R. Zollinger, Boston.—p. 27.
Benign Stricture of Bile Ducts Treated with Vitallium Tube. H. E. Pearse, Rochester, N. Y.—p. 37.
Adhesions from Hot Laparotomy Pads. F. E. Kredel and H. G. Smithey. Charleston, S. C.—p. 45.
*Late Results in Acute Perforated Peptic Ulcer Treated by Simple Suture: Particular Reference to Multiple Ulcer. E. F. Parker, Charleston, S. C.—p. 49.
Surgical Management of Postradiation Scars and Ulcers. H. Conway, New York.—p. 64.
Should Pleural Space Be Reduced in Size in Resection of Lung Tissue? Experimental Study. R. A. Rasmussen, W. E. Adams and L. S. Hrdina, Chicago.—p. 85.
*Effect of Replacement Therapy in Experimental Shock. J. E. Dunphy and J. G. Gibson 2d, Boston.—p. 108.
Reactions to Local Anesthetic Agents: I. Experimental Studies with Procaine. H. B. Shumacker Jr., Baltimore.—p. 119.
*Id.: II. Clinical Report. H. B. Shumacker Jr., Baltimore.—p. 134.
Mobilization and Deposition of Bone Calcium by Electrolysis: Preliminary Report. C. W. Walter, K. K. Van Slyke and C. Hufnagel, Boston.—p. 145.

Perforated Peptic Ulcer.—Parker states that, from 1921 through 1938, 52 patients with acute perforated peptic ulcer treated by immediate operation were admitted to the Roper Hospital. Of these, 25 survived and 27 died. Eighteen of those who survived could be traced, and in all of them the treatment was immediate operation with simple suture. Other procedures (cauterization with the actual cautery or iodine) in addition to simple suture were performed preliminary to simple suture in 5 of the 18 patients. Six of the patients considered themselves well from one to nine years after operation; they were able to work, were free from pain and vomiting, little or no care regarding the diet was needed and roentgen examination of the stomach and duodenum after a barium sulfate meal showed no evidence of an active peptic ulcer. The other 12 patients from seven months to eight years postoperatively considered themselves "not well." They continued to have, or had at some time subsequent to the primary operation, symptoms attributed to the persistence or recurrence of a peptic ulcer or its complications. Six patients were subjected to secondary operation, 3 because of a subsequent acute perforation. In these 3 the second perforation occurred from one to five years following the primary perforation. The other secondary operations were gastroenterostomies; in 1 for pyloric obstruction two years after the primary operation and in 2 for persistent symptoms one and two years following the primary operation. The author believes that the most likely reason for the poor results would seem to be the existence of multiple peptic ulcers in an appreciable percentage of these patients. One of the patients of the series, having two perforations, had a pyloric ulcer at the primary operation and a gastric ulcer at the second operation. The significant incidence of multiple ulcers, or scars considered to be the result of previous peptic ulceration, is further borne out by a study of pathologic material in which 16 of 44 cases presented evidence of multiplicity. Granting that the incidence of multiple peptic ulcer is significant, the wisdom of routine simple suture of perforated peptic ulcers might be questioned. The late results for the other types over simple suture are reported as better, and those for primary gastric resection the best. However, the primary consideration is survival of the patient and for this simple suture is the easiest, quickest and safest method, and it affords the patient the best possible chance of immediate recovery at any stage following perforation. Any further curative procedure subjects unnecessarily 50 per cent of the patients to additional risks. These patients should have long follow-ups at frequent intervals and, in the event of a subsequent complete pyloric obstruction without an additional ulcer, gastroenterostomy is highly successful and, if symptoms persist or recur, secondary gastric resection is recommended.

Therapy in Experimental Shock.—In correlating the physiologic effects of fluid replacement with the pathologic changes in experimental shock, Dunphy and Gibson find that replacement therapy instituted in the late stages has no effect on the pathologic tissue changes even though it restores the blood volume to normal. In early shock a single infusion of saline solution, in an amount calculated to raise the blood volume to normal, is not only of temporary benefit but causes such a dilution of plasma proteins that the late tissue changes are accentuated. Under the same circumstances the beneficial effects are also only of short duration and do not alter the pathologic changes. A continuous infusion of plasma, begun early in the experimental period, maintains the blood volume at normal levels and ameliorates the late tissue changes in shock. The amount of plasma needed for this is considerably in excess of that generally used in treating patients.

Reactions to Local Anesthetic Agents.—Shumacker discusses the local reactions, and their prevention and treatment, to the many lipoid soluble alkaloids used as local anesthetic agents. The reactions are of two types: those presumably dependent on the patient's hypersensitivity to the drug and those resulting from the absorption of a toxic dose. For the first type of reaction epinephrine or ephedrine should be of some therapeutic aid. The incidence of mild toxic reactions (characterized by restlessness, palpitations, perspiration, pallor, loquacity, nausea and tremor) may be reduced substantially by preliminary medication with one of the barbiturates. These reactions are also treated successfully with the barbiturates. In the severer reactions, characterized by convulsions and respiratory failure or by sudden collapse, the barbiturates are apparently effective prophylactically and therapeutically in the first type of severe reaction but of no value in the second. In human beings, as in laboratory animals, the duration and character of the reaction depend on the rate of absorption and the amount of anesthetic absorbed. A "safe" dose is unknown; a safe dose in most cases may in a rare instance prove fatal. Dilute solutions should be used, as anesthesia is likely to be obtained with an actually smaller amount of the anesthetic, for in ordinary infiltration a certain volume is necessary before anesthesia is satisfactory. Also if some of it is inadvertently injected into the blood stream a dilute solution is less apt to prove fatal. Epinephrine, except when contraindicated, should be mixed with the anesthetic solution because the combination slows absorption and increases the duration of the anesthesia. There are differences in the absorption rates from the various tissues and cavities of the body; therefore smaller amounts of anesthetic solutions should be used in those tissues in which the lethal dose is known to be small. The fatal dose may be less in elderly and very ill patients and in those with poor circulation and reduced function. Large amounts of local anesthetics should not be used to supplement general anesthesia. Until more specific aid is had, sudden reactions associated with early collapse should probably be treated by intravenous injection of epinephrine and a cardiorespiratory stimulant, such as a 25 per cent solution of nikethamide or metrazol. If the pulse has disappeared the injection should be made into the heart.

Tennessee State Medical Assn. Journal, Nashville

34:249-292 (July) 1941

Diagnosis of Rheumatic Fever in Children. S. Gibson, Chicago.—p. 249.
Treatment of Shock, with Particular Reference to Use of Blood Plasma. A. Blalock, Nashville.—p. 254.
Injuries at Wrist Joint. R. R. Brown, Nashville.—p. 258.
Gastrointestinal Hemorrhage. B. Malone 2d, Memphis.—p. 265.
Acne Vulgaris. H. King and C. M. Hamilton, Nashville.—p. 272.

Texas State Journal of Medicine, Fort Worth

37:201-266 (July) 1941

Hypertension in Pregnancy. E. D. Plass, Iowa City.—p. 208.
Analgesia in Obstetrics: Analysis of 500 Consecutive Cases. L. E. Arnold, Dallas.—p. 211.
Congenital Atresia of Cervix: Report of Case with Operative Correction. M. W. Sherwood and T. Speed, Temple.—p. 215.
Incidence of Ectopic Pregnancy in Negro: View of 8 Weeks Fetus in Unruptured Amniotic Sac. D. H. Hardin, Dallas.—p. 219.
Survey of Abortions at Parkland Hospital. J. McIver and J. C. Rucker, Dallas.—p. 221.
Diagnosis and Treatment of Acute Pancreatitis. L. S. Fallis, Detroit.—p. 223.
Electric Shock Therapy: Preliminary Report. A. Hauser, Houston, and L. Barbato, Galveston.—p. 228.
Acute Catarrhal Mastoiditis. C. C. Cody Jr., Houston.—p. 233.
Treatment of Metastatic Cervical Lymph Nodes: New Method. C. L. Martin, Dallas.—p. 236.
Controlling Colostomies. T. E. Smith, Dallas.—p. 241.
Asthenopia and Vitamin A Deficiency. T. J. Vanzant, Houston.—p. 246.
Significance of Qualified Professional Personnel in Advancement of Public Health. W. S. Leathers, Nashville, Tenn.—p. 248.

War Medicine, Chicago

1:463-610 (July) 1941

Disease Expectancy in the New Army. O. H. P. Pepper, Philadelphia.—p. 463.
*Refractory Gonococcic Infections: Elimination by Combined Artificial Fever and Chemotherapy as Related to Military Medicine. D. L. Rose, H. W. Kendell and W. M. Simpson, Dayton, Ohio.—p. 470.
Military Field Sanitation. W. A. Hardenbergh, Washington, D. C.—p. 479.
Medical Aspects of Selective Service System. M. S. Saslaw, Camp Shelby, Miss.—p. 486.
Rapid Identification of Gas Gangrene Anaerobes. G. B. Reed and J. H. Orr, Kingston, Ont., Canada.—p. 493.
The Navy and Social Hygiene in National Defense. E. W. Brown, New York.—p. 511.
*Treatment of Shock in Wartime. H. N. Harkins, Detroit.—p. 520.

Gonococcic Infections Resistant to Sulfanilamide.—Rose and his associates summarize their experiences in treating gonococcic infections refractory to sulfanilamide and its derivatives by means of combined artificial fever and chemotherapy. They emphasize the value of such a procedure in the prompt and certain eradication of gonorrhea among military and naval personnel. Their series consists of 105 patients with gonorrheal complications who were either resistant or intolerant to sulfanilamide and its derivatives. Of 9 patients receiving an eight hour session of fever at 106.6 F., only 1 was bacteriologically normal after a single session. Only 7 of 11 patients were rid of the infection after a single ten hour session at 106.6 F. As a control, 5 consecutive patients were hospitalized and further treated with a sufficient quantity of sulfanilamide to maintain the sulfanilamide level in the blood between 10 and 12 mg. per hundred cubic centimeters for ten days. At the end of this period all 5 patients still presented active clinical symptoms of gonorrhea. The genital secretions yielded abundant growths of Neisseria gonorrhoeae. All of them were then cured with fever therapy. Twenty patients received ten hours of fever at 106.6 F. and sulfanilamide orally during the preceding eighteen hours, after which no patient presented clinical or bacteriologic evidence of gonococcic infection. Of 16 patients given sulfanilamide intravenously immediately before the ten hours of fever at 106.6 F., only 13 were cured. Therefore the authors concluded that the mere presence of sulfanilamide in excess of 1 : 10,000 concentration at the time the fever was given was not sufficient for cure and that it appeared necessary for the drug to be present in the body fluids for several hours before the fever session. Eleven patients were given promin (diaminosulfone glucoside) intramuscularly during ten hours of fever at 106.6 F, and only 7 were cured after a single session of fever, indicating that there were no advantages in the concurrent use of promin and fever over a like amount of fever alone. However, all the 11 patients receiving ten hours of fever at 106.6 F. combined with promin administered intramuscularly during the preceding eighteen hours were cured after a single session of combined treatment. Also 7 patients receiving promin intramuscularly during the eighteen hours preceding a ten hour session of fever reduced to 106 F. were cured. The 4 patients receiving promin and the 11 sulfathiazole orally during the eighteen hours preceding eight hours of fever at 106 F. were also cured. This suggests that it is immaterial whether sulfathiazole or promin is given prior to the fever session. The total period of hospitalization for the patients in the later groups did not exceed forty-eight hours. The advantages of effecting a certain cure of gonococcic infection in such a short time are apparent.

Shock.—Harkins discusses the treatment of shock in wartime on the basis that it is a progressive vasoconstrictive oligemic anoxia. Its initiating factor is injury, whether traumatic, manipulative, thermal or chemical. The factors accompanying shock are oligemia, diminished blood flow, decreased cardiac output, decreased metabolism, tissue anoxia, capillary congestion, acapnia and acidosis, decreased muscle tonus, decrease in venous pressure, low blood pressure, vasoconstriction and hemoconcentration. Oligemia is possibly the most important of all these factors, and treatment in civil life or in wartime should begin before the condition has progressed irrevocably; the oligemia should be corrected and further loss of fluid prevented, and an adequate oxygenation of the tissues should be maintained until the patient's own improved blood volume and circulation cause the anoxia to disappear spontaneously. Preserved blood and blood plasma transfusion are the fluids with which prompt and concerted treatment is possible.

Western J. Surg., Obst. & Gynecology, Portland, Ore.

49:365-418 (July) 1941

Persistence and Recurrence of Toxic Goiter Following Subtotal Thyroidectomy. W. O. Thompson and F. W. Preston, Chicago.—p. 365.
Hyperthyroid Crisis. J. K. McGregor, Hamilton, Ont., Canada.—p. 367.
Diagnosis and Treatment of Sterility: Analysis of Newer Methods and Results in 133 Cases. W. M. Silbernagel and R. S. Fidler, Columbus, Ohio.—p. 371.
Appendical Femoral Hernia. R. B. McCarty, Riverside, Calif.—p. 376.
Secondary Operations on Biliary System After Cholecystectomy. R. D. Forbes, Seattle.—p. 380.
*Hyperparathyroidism. H. S. Chapman, Stockton, Calif.—p. 386.
Heterotopic Endometriosis. E. A. Parsons, Los Angeles.—p. 398.
New Form for Histories. C. Baumeister, San Jose, Calif.—p. 402.
Remarks on Subacute Bacterial Endocarditis, with Special Reference to Its Recognition and Present Status of Treatment. G. Blumer, New Haven, Conn.—p. 406.

Hyperparathyroidism.—Chapman discusses a case of hyperparathyroidism in a woman aged 41 in whom occurred progressive arthritic pains, loss of weight and exhaustion. Roentgen examinations disclosed a wide distribution of skeletal lesions. On surgical intervention, a large adenoma of the right lower parathyroid gland was found. Parathyroidectomy was done, and the patient kept on a high calcium diet, large doses of vitamin D and sunlight. Five years later roentgenograms showed recalcification but also the continued presence of large cystlike areas, generally surrounded by firm hard bone. According to the literature, the highest incidence of hyperparathyroidism occurs between the ages of 40 and 60 and predominates in females. Single adenomas are far more common than hyperplasia and are found six times oftener in the lower parathyroid glands, the right lower gland constituting the gland of choice. Early diagnosis is difficult and the clinical picture is most varied. It includes hypercalcemia, precordial pain, weakness, dyspnea and edema, neurologic signs, fractures, anemia, vomiting, dysentery, calculi and evidence of mental deterioration. A disturbance in the calcium and phosphorus metabolism is at present the only definite basis for diagnosis. Hypercalcemia is always present. Contemplated surgical intervention should be based only on positive diagnosis. The surgeon will encounter either (1) an adenoma, (2) hyperplasia of one or more glands or (3) generalized hyperplasia of all glands. In most cases hypocalcemia follows parathyroidectomy, and tetany may be expected. Recalcification should begin within a short time after the operation and may induce tetany of recalcification. Reparative changes following parathyroidectomy are slow.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

Annals of Rheumatic Diseases, London

2:167-230 (June) 1941

Present Status of Ligue Internationale contre le Rhumatisme. R. Pemberton.—p. 169.
Recent Studies on Arthritis and Rheumatism in the United States. P. S. Hench.—p. 172.
Study of Certain Blood Tests Which Reveal Colloidal Abnormalities in Rheumatic Conditions. H. L. Milles and H. B. Salt.—p. 192.
Observations of Rheumatic Diseases Under War Conditions. O. Savage. —p. 211.
Observations on Respiration in Articular Cartilage. M. A. Bowie, O. Rosenthal and G. Wagoner.—p. 216.

British Journal of Ophthalmology, London

25:305-348 (July) 1941

Tuberous Sclerosis with "Phakomas": Case. J. P. Martin and L. H. Savin.—p. 305.
Epidemic Superficial Punctate Keratitis in Malaya: Account Based on Observations of Superficial Punctate Keratitis Which Occurred in Selangor, One of the Federated Malay States, from 1935 to 1938. A. Viswalingam.—p. 313.
Infection of Sphenoidal Sinuses with Secondary Affection of Eyes, Causing in One Detachment of Retinas in Both Eyes and in the Other Acute Optic Neuritis of One Eye. E. W. Arndt.—p. 324.
Robert Brudenell Carter. R. R. James.—p. 330.

British Journal of Urology, London

13:43-126 (June) 1941

Genital Tuberculosis in the Male. T. E. Hammond.—p. 43.
Concerning Papillomas of Bladder. V. Z. Cope.—p. 74.
Notes on Topography of Kidney. T. Zondek.—p. 83.

Lancet, London

1:811-838 (June 28) 1941

*Cutaneous Anthrax. A. E. Hodgson.—p. 811.
Effort Syndrome. M. Jones and A. Lewis.—p. 813.
*Intravenous Ascorbic Acid in Experimental Acute Hemorrhage. C. P. Stewart, J. R. Learmonth and G. A. Pollock.—p. 818.
Coronary Hemorrhage: Case. J. Mackay.—p. 820.

Cutaneous Anthrax.—Hodgson treated 93 cases of cutaneous anthrax with anthrax serum without excising the lesion. Fifty-two of the patients were given large doses of serum intravenously; 6 of these died, but 4 of them were hopelessly toxic when first seen. The other 41 patients, none of whom died, were given serum and a British made neoarsphenamine (neokharsivan). Many of these 41 patients were gravely ill when they were admitted to the hospital. The author believes that, when conditions are reasonably suggestive of anthrax infection, treatment should not be delayed for final proof but from 5 to 20 cc. of anthrax serum should be injected intramuscularly. It is an entirely empiric procedure, but he has carried it out in 37 instances in which farmers and animal slaughterers with abraded hands have handled carcasses dead of verified anthrax, and in none of them has the disease developed. It can do no harm and may do good. Arsenical therapy should be regarded solely as an adjuvant to serum therapy, and only in the mildest cases in which infection is favorably located or when serum is not available is it to be used by itself.

Ascorbic Acid Intravenously for Acute Hemorrhage.—Stewart and his associates gave ascorbic acid intravenously to cats in an effort to increase tissue oxygen in experimental acute hemorrhage. They produced the hemorrhage by removing half of the volume of blood through a cannula. This was calculated as 6 per cent of the body weight. The intravenous injection of ascorbic acid prolonged the life of the animals. The benefit to be expected from 1 grain (0.065 Gm.) of sodium ascorbate in 6 cc. of physiologic solution of sodium chloride is at least as great as that from a much larger volume of physiologic solution of sodium chloride or isotonic dextrose solution. Eight of 11 animals survived the strain of the bleeding for longer than one hour and forty minutes. The volume of fluid replaced (6 cc.) cannot play a part in promoting this temporary recovery. The temporary improvement is probably due to an increased availability of oxygen for the tissues. The problem is being investigated more fully. Certain combinations of substances (ascorbic acid-glutathione) may be even more effective. It has been suggested that the addition of lobeline might increase the usefulness of such intermediate hydrogen carriers. The authors intend to test the efficacy of ascorbic acid intravenously in injuries from air raids. They suggest a dose of 3 grains (0.2 Gm.) of the acid in not more than 10 cc. of solvent. The type of patient to be benefited is one pinned under wreckage who can be reached, a vein identified and the injection given, or the casualty to whom it is not possible to give an immediate transfusion of blood or plasma. They suggest that the injection of ascorbic acid may keep certain patients alive until blood or plasma transfusion is possible.

Medical Journal of Australia, Sydney

1:773-794 (June 28) 1941

Some Considerations in Treatment of Wounds. H. R. G. Poate.—p. 773.
Treatment of Varicose Veins and Their Complications. A. F. Hobbs. —p. 776.
Relationship Between Doctor and Patient. A. E. Brown.—p. 779.
*Lung Blast. T. F. Rose.—p. 784.

Lung Blast.—Rose states that postmortem studies show that hemorrhages in pulmonary concussion or "lung blast" are due to the sudden and violent impact of the blast wave of high explosives on the wall of the chest. The extent and location of the lesions will depend on the size of the exploding bomb, the protection afforded by buildings or other objects and by the casualty's position in relation to the blast wave. A person facing an exploding bomb may have both lungs affected anteriorly, one with his back toward the explosion will have both lungs affected posteriorly, and one with his side to the blast will have one lung affected. The author divides lung blast into three types: patients found dead immediately after an explosion who have no outward bodily injury, those with grossly affected lungs who usually do not show signs of injury until some time after the trauma has been sustained (these patients' general condition never seems satisfactory from the start, although no cause for it can be found) and those with less severe concussion who usually recover. The first suggestion of lung blast in these last casualties may be a dry cough accompanied by a rise in temperature and possibly some pain in the chest. The rise in temperature is due to trauma and resolution of extravasated blood. The temperature, pulse and respiratory rate rise as the condition progresses and then fall slowly as the patient improves. In these less severe cases the physical signs in the chest are areas of crepitation with normal breath sounds, replaced in from twenty-four to forty-eight hours by areas of tubular breath sounds and impaired percussion note. These signs may clear up in the next four days or may last longer. The condition may be difficult to diagnose from other closed injuries of the lung: pneumonia. Roentgenograms will reveal mottled woolly shadows which correspond to the hemorrhagic areas. Further roentgen study will reveal an increase in the size or a disappearance of these shadows, according to the progress of the patient. The ideal would be to take roentgenograms of the chests of all persons exposed to a bomb detonation, thus revealing lung blast before clinical signs appear. Patients who have been near an exploding bomb even after shock disappears should be kept in the hospital for at least twenty-four hours to avoid their being discharged with an as yet unrevealed lung blast. If anesthetics are needed for wounds requiring surgical attention, they should be administered intravenously and should not be irritating to the lungs. Pentothal sodium is suggested. Too much intravenous medication may produce a waterlogged condition of the lungs and further embarrass respiratory efficiency. For the revealed case of lung blast, treatment is not unlike that for pneumonia. Sulfapyridine may be useful in preventing infection of the damaged areas. Unless absolutely necessary, these patients should not be moved from one hospital to another. The immediate prognosis depends on the category in which the patient falls. Death within a few days of the explosion is especially apt to occur if the condition is not recognized and the patient is not confined to bed.

Revista de Tuberculosis del Uruguay, Montevideo

9:215-284 (No. 3) 1940. **Partial Index**

*Pleural Lavage and Intrapleural Aspiration in Tuberculous Empyema. J. A. Sciuto.—p. 254.

Treatment of Tuberculous Empyema.—Sciuto advises repeated pleural lavage and aspiration in closed infected tuberculous empyema. The fluid is aspirated by puncture. The lavage is performed slowly with 3 or 4 liters of concentrated Jessen solution (iodine 1 Gm., potassium iodide 4 Gm., distilled water 4 liters). It is followed by continued aspiration, the duration of which varies from one to twenty-four consecutive hours, depending on the size of the pleural cavity, the elasticity of the pleura and the virulence of the infection. The treatments are given three or four days apart. The treatment is continued as long as the lung continues to expand, which may be several weeks or months. If reexpansion does not take place, surgical intervention is indicated. In cases of infected tuberculous empyema with a fistula, intrapleural aspiration without lavage is indicated. Intrapleural lavage with aspiration or aspiration alone favorably alters the nature and constitution of the empyema fluid, controls fever, improves the appetite and general condition of the patient and counteracts collapse of the lung. Even if the treatment fails to control the collapse, the improvement in the empyema and the general improvement place the patient in a better condition to withstand surgical intervention.

Monatsschrift für Kinderheilkunde, Berlin

87:1-400 (March 24) 1941. **Partial Index**

Vitamin C. F. Widenbauer.—p. 12.
Pathogenic Bacteria and Vitamin C. J. v. Gagyl.—p. 41.
K Avitaminosis in the Newborn. Dam and P. Plum.—p. 55.
*Mass Experiment with Prophylactic Administration of Massive Dose of Vitamin D_2. P. Frick.—p. 66.
Treatment of Alimentary Toxicosis of Nurslings During First Three Months of Life. W. Bayer.—p. 97.
*Bacteriology, Epidemiology and Therapy of Meningococcic Infections. W. Goeters.—p. 144.
*Predisposition to Poliomyelitis. H. Müller.—p. 263.
Virus Diseases of Central Nervous System. H. Kleinschmidt.—p. 272.

Prophylactic Use of Massive Dose of Vitamin D_2.—Frick states that large doses of vitamin D_2 administered to 1,759 infants produced no harmful effect, not even in infants who had previously been given repeated small doses. In some instances one dose of 7.5 mg. of D_2 was not enough to prevent rickets during the entire period when there was little sunshine. Even a single dose of 15 mg. of D_2 was not always enough. A single dose of 15 mg. did not prove superior to a single dose of 7.5 mg. The degree of efficacy was about 90 per cent with either of these doses. He advises that one dose of 7.5 mg. be given to all infants in October, while a second dose of 7.5 mg. should be given later in the season to infants who begin to show rachitic symptoms. The author gained the impression that two administrations of 7.5 mg. are better than a single one of 15 mg. in the infants who are likely to develop rickets.

Meningococcic Infections.—Goeters reports observations on 138 children with epidemic meningitis. Pathogenic organisms were detected in 87 per cent; many of the meningococcus strains were facultative anaerobes. Simultaneous aerobic and anaerobic culture, particularly after preliminary enrichment in ascitic bouillon, improves the results of the culture method. The demonstration of causal organisms in the cadavers of children who died of meningococcic infection was more successful from sternal marrow than from the heart blood. The sporadic cases of meningitis have the most unfavorable prognosis. Mortality rate decreases in the course of an epidemic, and this must be taken into consideration in evaluating treatment. Type determination suggests that this decrease in mortality rate during an epidemic is due partly to a decrease in the virulence of the pathogenic organism. Thus, whereas type I caused severe forms of meningitis in 1939, it caused mild cases in 1940. In an epidemic caused by type VI, the first cases were usually severe and fatal, but later the same type caused only abortive forms. Serums, repeated blood transfusions, insufflation of air into the lumbar sac, and irradiation failed to exert a therapeutic effect. Sulfanilamide and azosulfamide were ineffective, but sulfapyridine proved highly successful. Early exhibition and large initial doses are decisive for the efficacy of sulfapyridine in meningococcic infections.

Predisposition to Poliomyelitis.—Müller made cutaneous tests, such as the Schick, Dick and tuberculin, of 43 children with poliomyelitis during the early acute stage and again after an interval of at least three weeks. In 29 the repeated tests gave different results from the first tests. It appears that something has happened before the onset of the poliomyelitis, an impairment or damage which may be of an infectious or a noninfectious nature. He concludes that the first elevation of the biphasic fever curve which precedes the central nervous symptoms in many cases is not caused by the poliomyelitis virus, since the virus is strictly neurotropic and is incapable of producing catarrhal symptoms in experiment. The fever and indisposition which precede true poliomyelitis by several days take the form in some cases of characteristic infectious disease such as measles, German measles, chickenpox or dysentery. In a considerable number of cases fever does not precede the meningitic symptoms and in such cases a noninfectious preceding impairment such as overexertion, trauma, journey or excessive sun exposure can often be demonstrated. The author was unable to detect a correlation between the nature of the preceding damage and the course of the poliomyelitis in a study of 400 cases. The severity of the damage seems to be of less importance than the constitution. The interval between the preceding trauma and the onset of the meningitic poliomyelitic symptoms could not be established in all cases. With the noninfectious trauma the interval was usually short, often less than twenty-four hours. With mild infections the interval varied between five and eight days and with the more serious infections it was over eight days. Trauma and other noninfectious damage produce short fluctuations in the antibody content, whereas infections cause longer ones. In the course of epidemics the virus, because of its ubiquity, infects a large number of persons and reaches the central nervous system during the period of incubation. However, infection of the central nervous system is not synonymous with disease. In the majority of cases the infection remains latent, in some the cerebrospinal fluid is altered and there are present fever and pains. In still another group some impairment takes place during the period of incubation; the fluctuation in immunity that follows this impairment interrupts the equilibrium between host and parasite, and the disease develops. Predisposition to every disease consists of different components, but in poliomyelitis the chief component seems to be the preceding trauma.

Wiener klinische Wochenschrift, Vienna

54:285-304 (April 4) 1941. **Partial Index**

New Method in Treatment of Chronic Articular Disturbances. B. von Mezö.—p. 288.
*Life Saving Thoracocautery in Tension Pneumothorax. J. Obstmayer. —p. 291.
Surgical Treatment of Epileptic Disorders. W. Sorgo.—p. 296.
Differential Diagnosis of Asthmatic Disorders. E. Risak.—p. 298.

Thoracocautery in Tension Pneumothorax.—Obstmayer states that thoracocautery may become a life saving measure in sudden valvular pneumothorax. In spontaneous pneumothorax with excess pressure, efforts must be made to determine the presence of adhesions by roentgenoscopy. If tuberculous adhesions are present and the film shows spotty-striped foci in both upper lobes, thoracoscopy should be done. If no cicatricial blisters are found, the process is probably a fused juxtapleural infiltrate. The pulmonary fistula must be closed if the patient is to be saved. The extending adhesions must be severed by cauterization and complete pulmonary collapse obtained. The pneumothorax should be maintained in order to influence the tuberculous process favorably. Thoracocautery must be employed as soon as possible, within a few hours after the development of the valvular pneumothorax, because the longer the fistula exists the greater is the danger of pleural infection.

Mitt. a. d. med. Akad. zu Kioto, Kyoto

31:697-1032 (March) 1941. **Partial Index**

*Arterial Thrombostomy and Arteriolysis in Spontaneous Gangrene of the Extremities. K. Imazu and J. Watanabe.—p. 697.

Arterial Thrombostomy and Arteriolysis in Buerger's Disease.—Imazu and Watanabe report the favorable results of treatment of 2 patients with Buerger's disease on whom thrombostomy and arteriolysis had been performed. The first patient, a man aged 61, had thrombostomy performed on the left external iliac artery; the second patient, a man aged 33, had undergone arteriolysis of the anterior tibial artery. In Buerger's disease with spontaneous gangrene or intermittent claudication there is usually an isolated thrombus about 2 to 2.5 cm. in length in the larger arterial trunk (from the external iliac artery to the bifurcation of the popliteal artery). Such a thrombus usually adheres to the vascular intima and cannot be removed. Under such circumstances thrombostomy is practiced, usually followed by satisfactory restitution of circulation, leading to recovery. The incision of affected blood vessels must be made always below, or distal to, the thrombus, over the normal vascular wall, and the thrombus is perforated in the proximal or central direction. This precaution is important, since the incision made above or directly over a thrombus will not only fail in controlling hemorrhage but often results in aggravation of clinical conditions. Thrombosis occurring in the tibial artery below the popliteal artery offers difficulty in this type of treatment, since the caliber of the vessel is small and the venous plexuses around the artery lead to profuse hemorrhage. For this reason the authors performed arteriolysis, which consisted in the removal of the adhesions between the artery and its surrounding tissues or the resection of the surrounding venules, thus removing the pressure on the artery. Injection of physiologic solution of sodium chloride into the thrombosed vessel has been found to have no therapeutic effect.

Okayama Igakkai-Zasshi, Okayama

53:679-902 (April) 1941. **Partial Index**

*Therapeutic Effect of Autogenous Blood Injection on Asthma, Urticaria and Cerebral Hemorrhage. K. Kondo and H. Kondo.—p. 880.
*Concerning Gold Exanthema. S. Ito.—p. 888.

Autogenous Blood in Allergic States.—The Kondos reported that one to three semiweekly injections of autogenous blood, given in amounts varying from 5 to 20 cc., produced clinical improvement in 6 out of 9 cases of urticaria of various degrees of severity; the remaining 3 cases showed little or no effect. In a total of 10 patients with bronchial asthma, two to five intramuscular injections of autogenous blood, in amounts varying from 5 to 30 cc., brought about noticeable improvement in all but 1 case. Observation on the suggested benefit of this type of treatment in cerebral hemorrhage is limited to 1 case, in which mild symptoms were relieved while severe attacks were unaffected by the injection treatment. The authors consider the therapeutic results of autogenous blood to be due to the stimulating effect of allergens as well as antiallergens, toxins and antitoxins, and other unidentified substances present in the patients' blood.

Gold Exanthem.—Ito reports a case of a gold exanthem in a 60 year old woman treated with intravenous injection of a gold salt preparation (Lopion) (0.05 Gm.) for lupus erythematosus discoides. Thirty hours after the injection the patient complained of a tingling sensation in the extremities, with a rise in temperature (102.2 F.) and a scarlatiniform rash over the distal portions of the arms and legs. No albumin, sugar or hyaline cylindroids were found in the urine. Within five days following intravenous injection of physiologic solution of sodium chloride the exanthem as well as the general symptoms completely disappeared. From the Japanese literature the author reviews 27 cases of similar reaction to various salts of gold and finds that in the majority of cases a gold exanthem developed after ten or more injections had been given, while in about 18 per cent of cases the rash appeared with but one injection.

Vrachebnoe Delo, Kharkov

22:721-848 (Nos. 11 & 12) 1940. **Partial Index**

Antiepidemic Campaign of Ukraine. F. V. Barinsky.—p. 723.
The Extent and Nature of Immediate Aid to Injuries of the Jaw. D. A. Entin.—p. 727.
Surgical Picture of Pulmonary Abscess. F. Yu. Rose.—p. 730.
Effect of Insulin on Liver Sugar Secretion and on Inhibition of Lactic Acid. S. G. Genes, P. M. Charnaya and T. S. Yakusheva.—p. 735.
Differential Diagnosis of Aleukemic Lymphadenosis. T. I. Meerzon, I. M. Marcus and E. A. Dutkevich.—p. 749.
*Diagnostic Significance of the Corneal-Pterygoid Reflex. A. B. Frenkel.—p. 759.

The Corneal-Pterygoid Reflex.—Frenkel investigated the corneal-pterygoid reflex in 967 persons, 747 of whom presented disease of the nervous system, 200 were normal adults and 20 were children below the age of 2 years. In persons with a normal nervous system, in neurotic patients and in those with disease of the peripheral nervous system or of the spinal cord the reflex was only seldom present (6 to 7 per cent) and when present was weak. A clearcut corneal-pterygoid reflex was observed only in the presence of a cerebral lesion. It was present with greatest frequency in syndromes involving the internal capsule or the motor cortical zone. It appears to be associated with a more or less acute pyramidal lesion. The reflex may be of considerable diagnostic value in cerebral coma, in which it may be quite active while other reflexes are diminished. The corneal-pterygoid is a reflex of the trigeminal nerve, and its reflex arc is normally inhibited by the pyramidal tracts. The reflex is a manifestation of synergism between the eye and the mouth. The functional relationship is explained on the basis of philogenetic existence of a single motor apparatus for the eye and the mouth. This apparatus in a later stage of evolution became separated into two distinct functioning apparatuses, that of winking and that of chewing.

Maandschrift voor Kindergeneeskunde, Leyden

9:343-384 (June) 1940

*Fetal Keratomalacia. H. D. Bouman and S. van Creveld.—p. 343.
Schizophrenia in Children. R. Vedder.—p. 352.
Pathogenesis of Postvaccinal Encephalitis. J. D. Verlinde.—p. 368.

Fetal Keratomalacia.—Bouman and van Creveld observed a mother, aged 16, who during the first six months of pregnancy had had an inadequate diet, particularly as regards vitamins. She had eaten mostly white bread and a margarine to which no vitamins had been added. She had had no milk or eggs and only once a week lean meat and greens. This mother gave birth to a child with such severe ocular changes that complete blindness will be the result. The authors regard the congenital eye defects as the result of fetal keratomalacia.

Nordisk Medicin, Stockholm

10:1271-1350 (April 26) 1941. **Partial Index**

Hospitalstidende

Tryparsamide Treatment of Neurosyphilis: Changes in Field of Vision: Gerstman Syndrome. G. K. Stürup and M. Thrane.—p. 1277.
*Cirrhosis of Thyroid Gland. J. Hertz.—p. 1290.
Azotemia and Chloropenia in Manifest Gastric Hemorrhages. A. Guldager.—p. 1298.
Intraperitoneal Neurinomas. J. Schousboe.—p. 1305.

Cirrhosis of Thyroid Gland.—Hertz says that cirrhosis of the thyroid is an enlargement of the thyroid gland due to a slow grade chronic inflammation of unspecific kind and that this entity includes the "iron hard" goiter described by Riedel and Hashimoto's "struma lymphomatosa." He reports 5 cases. From the literature and his cases he is inclined to believe that the different cases represent the same disorder treated at different stages. The diagnosis of cirrhosis of the thyroid is extremely difficult; it has not been made before operation, and then usually not until after microscopic examination. First of all cancer, but also tuberculosis, syphilis, woody phlegmon and lymphogranulomatosis, must be excluded in the differential diagnosis. The normal or but slightly affected sedimentation reaction, the relatively good general condition and the absence of metastases are helpful toward correct diagnosis. Treatment is radical removal because of the suspicion of a malignant condition. The prognosis is good.

Book Notices

Essentials of Gynecology. By Leo Brady, M.D., F.A.C.S., Assistant Professor of Gynecology, University of Maryland, Baltimore, and Ethna Louise Kurtz, R.N. Fabrikold. Price, $2.75. Pp. 257, with 58 illustrations. New York: Macmillan Company, 1941.

This is a fine little book. The authors present the elements of gynecology in a pleasant, readable and accurate manner. Actually, "Elements of Gynecology" might be a more accurate title. Sufficient attention is given to gynecologic anatomy and physiology and there is a full section on female urology. The common and uncommon gynecologic diseases are discussed with an excellent sense of proportion. Easy simplicity constitutes the literary style. Max Brödel's marvelous illustrations are familiar to older readers and retain their pristine interest. The volume has been pleasingly assembled by the publishers. It is small, has good paper and large print, and the cover is semi-flexible. The work is suitable for student nurses (being written for them), for third year medical students as a preliminary survey of gynecology, and there is a third and uncommon place of usefulness for the volume: because of its vocabulary and its clear information it would be an ideal book for the gynecologist's secretary to read. Incidentally, when the book is republished it might be well to supplement the rather brief index with a short gynecologic glossary, including a little etymology. A page or two of sketches or photographs of gynecologic instruments might be helpful to student nurses also. In conclusion it may be remarked that, although the notes on nursing technic necessarily center about Miss Kurtz's experience in Baltimore, there is a spirit of generalization which will enable nurses anywhere to read her chapters with profit.

Medical Diagnosis and Symptomatology. By Samuel A. Loewenberg, M.D., F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. Fifth edition. Cloth. Price, $12. Pp. 1,139, with illustrations. Philadelphia: F. A. Davis Company, 1941.

"Medical Diagnosis and Symptomatology," the fifth edition of "Diagnostic Methods and Their Interpretation in Internal Medicine," is characterized by a complete alteration in the format of the text, extensive revisions in content, the addition of much new material including chapters on the vitamins, allergy and geriatrics, and the introduction of numerous new electrocardiograms, roentgenograms, colored plates and photographs. Prominent errors present in the previous edition have in large measure been rectified, but numerous erroneous and careless statements still persist. Thus on page 257 the author defines orthopnea as extremely difficult breathing. Figure 40, a four lead electrocardiogram designed to show right ventricular preponderance, in reality demonstrates a 180 degree axis shift. The statement that in auricular fibrillation "the faster the heart rate the more irregular it becomes" and further "there is always a pulse deficit" is both obscure and misleading (p. 430). On page 737 the author notes that "syringomyelia . . . is characterized by inflammation of the spinal cord," although present concepts would indicate that the disease is most probably due to a congenital neural defect, a developmental anomaly of the central canal. The statement on page 687 that in focal glomerulonephritis "edema only moderate . . . hypertension marked . . . blood chemistry shows marked retention of urea nitrogen, nonprotein nitrogen . . ." is not consistent with current opinion. The discussion of hypertension on pages 411 and 412 is inexcusably brief when compared with the space devoted to other subjects, and no acknowledgment is made of recent fundamental developments in this field. The classification of the nephritides on page 686 is extremely incomplete, a striking omission, for example, being the failure to make any mention of pyelonephritis. The necessity of attempting to incorporate a tremendous amount of material in a volume of limited scope precludes the possibility of devoting adequate attention to essential material and leads consequently to inevitable albeit unintentional superficiality. In a textbook designed to aid in the diagnosis of medical disease, such relatively brief rediest of well known facts is none too valuable. The volume is accordingly of little assistance to medical student, general practitioner or specialist.

Otchet o nauchno-issledovatelskoy rabote Vsesoyuznogo Instituta Eksperimentalnoy Meditsiny im. A. M. Gorkogo za 1933-1937 gg. Otvetstvenny redaktor: L. N. Fedorov. [Report on Scientific Research of Allsoviet Institute of Experimental Medicine During Years 1933-1937.] Cloth. Price, 35 rubles. Pp. 575, with illustrations. Moscow & Leningrad: Narkomzdrav SSSR, Gosudarstvennoe Izdatelstvo Meditsinskoy Literatury "Medgiz," 1939.

This large volume tells the story of the Allsoviet Institute of Experimental Medicine. In 1870 there was founded in St. Petersburg the Institute for Experimental Medicine, headed by the most prominent scientists in the various fields of medicine. This was the only research institute under the old régime. The work of the institute was constantly hampered by the parsimony of the government so that, for example, Pavlov's laboratory had to depend to a great extent on private contributions. From the beginning of the new régime the institute was considerably enlarged. A special biologic station was created for Pavlov outside the city of Leningrad. In 1932 it was decided to reorganize the institute into Allsoviet Institute for Experimental Medicine, the aim of which was to be "a many sided study of the human organism in health and in disease." Affiliates of the institute were founded in Moscow and in Sukhumi. In 1935 the seat of the institute was transferred to Moscow, the Leningrad Institute remaining an affiliate. The work of the new institute was to embrace the following phases: (1) infectious diseases such as typhus, dysentery, diphtheria, brucellosis, tetanus, leishmaniasis and helminthiasis; (2) cancer and tuberculosis; (3) physiology and pathology of digestion; (4) atherosclerosis; (5) physiology and pathology of the higher nervous activity, morphology of the nervous system and the sensory organs; (6) neurohumoral regulation; (7) evolutionary physiology and morphology; (8) normal and pathologic metabolism; (9) effect on the organism of physical factors. The work of the institute likewise embraced the production of vaccines against typus, typhoid, paratyphoid and tetanus. The epidemiologic studies included the pathogenesis and early diagnosis of brucellosis, the study of vectors of recurrent fever, tularemia and pappatachi fever. Continuation of Pavlov's researches are represented by studies of evolutionary physiology of the nervous system under Orbelli, studies of the physiology of the digestion under Razenkov and the study of nervous trophism under Speranskiy. An interesting and new departure is the study of the physiology of the sensory organs under the leadership of Professor Propper-Grashchenkov. The well known method of angiostomy of Professor London contributed much to the solution of a number of questions in the intermediate metabolism.

The present volume is a report on the activities of the institute for the past five years. The work of each department is presented in the form of a review with an appended list of contributions from the co-workers. By way of criticism it is pointed out that closer correlation is to be desired between the institute and its affiliates and the actual practice of medicine. It is also pointed out that the work of postgraduate training of doctors in basic branches such as microbiology, pathology, biochemistry and pharmacology is desirable. It is evident that the government was liberal in appropriating funds for the work of the institute. The quality of the research is on a par with that of the best institutes of this type.

Novas contribuições ao estudo do pênfigo foliaceo (fogo-selvagem) no estado de São Paulo. Pelo director do serviço João Paulo Vieira. Trabalho do serviço do pênfigo foliáceo. Subordinado a diretoria do serviço da lepra no E. de S. Paulo. Serviço criado pelo Interventor Adhemar de Barros, decreto 9.523 de 17 de Setembro de 1938. Paper. Pp. 242, with 105 illustrations. São Paulo: Emprêsa Gráfica da "Revista dos Tribunais," 1940.

Endemic in certain regions of Brazil is a pemphigoid disease designated pemphigus foliaceus because of its dermatologic features and known by the natives as fogo-selvagem (wild fire) because of its subjective accompaniment of burning. Vieira published a study of this entity in 1937 and the present monograph summarizes comprehensively his observations up to date. Written in Portuguese with a French translation appended, the text is supplemented with numerous illustrations of cases, reproductions of roentgenograms, photomicrographs, maps of distribution of the disease and statistical tables. Despite identity of name and likeness of morphology, the South American disease is probably different from the pemphigus foliaceus familiar to dermatologists in this country—the "classic" form described

nearly a century ago by Cazenave. Evidence points to an infectious agent in the etiology of fogo-selvagem, and Vieira's epidemiologic studies suggest that a species of mosquito and possibly also certain insect parasites of indigenous bats are deserving of suspicion as vectors. Inoculation experiments by the author were unsuccessful in transmitting the disease to laboratory animals. This result, it may be recalled, is in contrast to that obtained by Lindenberg, who in 1937 reported the transfer of the disease to rabbits from the blood of patients. Repetition and evaluation of these experimental investigations seem to be indicated. Clinical features of fogo-selvagem are portrayed minutely. Of special interest is the detailed subclassification of nine varieties of the chronic form of the disease. Present also are chapters dealing with results of exhaustive laboratory examinations, histopathologic findings in the skin, and data on the author's therapeutic experiences. This volume will be read with advantage by dermatologists and students of tropical medicine. The addition of a bibliography, unfortunately lacking, would enhance the value of this contribution.

Technik und Ergebnisse der Lippenplastik. Von Dr. Georg Axhausen. Paper. Price, 13.50 marks. Pp. 112, with 233 illustrations. Leipzig: Georg Thieme, 1941.

Axhausen has written this book on the repair of cleft lips as a sequel to his cleft palate publication (Gaumenplastik) of 1936. The work begins with a brief discussion of various methods he has used, including those of Hagedorn, Lindemann, Blair and Brown, and Veau and Plessier, and then proceeds with the description of his own method used in total single clefts. He prefers to close the clefts around the age of 8 to 12 weeks. A small septal flap and one from the lateral wall of the nasal cavity are sutured together to form the floor of the nose. Incisions are then made in each buccal fornix with undermining of the alae and cheeks, and a lateral cut is made just beneath the ala out toward the cheek on the cleft side. The lip and nostril are then rotated into place and held with a catgut retention suture, which is anchored around the nasal spine and engages the lip musculature on the cleft side. The skin is closed in a vertical straight line with or without interdigitation of small vermilion flaps. The muscle and mucosa are closed in separate layers. Partial clefts are treated by a V excision and closure, reliance being placed on the retention suture around the nasal spine. Double clefts are closed in much the same manner as the total single clefts, one side being closed at the first operation and the other side about four weeks later. The vermilion of the prolabium is utilized, giving a pronounced notching on each side. Many of the single repairs illustrated also have some notching of the vermilion, but the author believes that this often disappears with growth. The concluding chapters deal with various secondary operations, ranging from excision of scars and adjustment of the vermilion to nasal reconstructions, switching of lower lip flaps and lower jaw resections. The illustrations are mostly of patients. The general plan of presentation is good. It is undoubtedly the most comprehensive recent work in the German literature on the subject.

Der Rheumatismus: Sammlung von Einzeldarstellungen aus dem Gesamtgebeit der Rheumaerkrankungen. Herausgegeben von Professor Dr. Rudolf Schoen, Direktor der Medizinischen Universitäts-Klinik und -Poliklinik Göttingen. Band XX: Behandlung rheumatischer Erkrankungen durch Anaesthesie. Von Dr. Egon Fenz, Primararzt, Vorstand der 1. medizinischen Abteilung im Versorgungsheim der Stadt Wien "Lainz." Boards. Price, 4.50 marks. Pp. 99, with 13 illustrations. Dresden & Leipzig: Theodor Steinkopff, 1941.

This book is based on observations of 651 cases of such varied conditions as neuritis and neuralgia, primary myalgia, bursitis, rheumatoid arthritis (arthrosis deformans in German) and spondylitis, treated by the use of local anesthetics. Of the entire group (given an average of three to four infiltrations with anesthesia) 70 per cent remained free or almost free from pain; only 7 per cent were totally unimproved. Although there was considerable variation between the response of the different groups, depending on the clinical diagnosis, the results as a whole seemed to be surprisingly favorable. This discussion deserves careful reading and checking in this country on an adequate scale, since, if the results can be confirmed here, it would constitute a real addition to therapeutic methods for this group of difficult conditions.

Der Rheumatismus: Sammlung von Einzeldarstellungen aus dem Gesamtgebiet der Rheumaerkrankungen. Herausgegeben von Professor Dr. Rudolf Schoen, Direktor der Medizinischen Universitäts-Klinik und -Poliklinik Göttingen. Band XXI: Rheumatismus und Frauenkrankheiten. Von Professor Dr. Heinz Küstner. Boards. Price, 2.10 marks. Pp. 38. Dresden & Leipzig: Theodor Steinkopff, 1941.

This booklet is one of a series of short monographs on various aspects of "rheumatism," under the editorship of Professor Schoen. In this publication the relationships between some of the joint, muscle and nervous complexes commonly considered to belong in the field of rheumatism are discussed from the standpoint of the gynecologist and the part which the female genital organs may play in the rheumatic problem. Perhaps the brevity of the pamphlet offers the best evidence of the rather tenuous connection which seems to exist between the female genital tract and rheumatic disorders.

Chemistry of Food and Nutrition. By Henry C. Sherman, Ph.D., Sc.D., Mitchill Professor of Chemistry, Columbia University, New York. Sixth edition. Cloth. Price, $3.25. Pp. 611, with 46 illustrations. New York: Macmillan Company, 1941.

The numerous previous editions of this volume have had tremendous use. It is one of the best available books on the subject by a recognized leader in the field discussed. The author keeps it constantly abreast of current knowledge. The extensive bibliographies associated with the various chapters indicate the vast reading on which the work is based. Particularly important is the extensive section on thiamine. However, even here the author has failed to provide the information of the last six months, which makes obsolete many of the statements that seemed authentic in the summer of 1940. So many factors govern human nutrition that constant revisions occur in our points of view.

Trudy I-oy Moskovskoy Psikhiatricheskoy Bolnitsy. Vypusk vtoroy yubileynly CXXX let. Pod obshchey redaktsiey: M. A. Dzhagarova. S predisloviem: Y. A. Gilyarovskogo i A. I. Vinokurovoy. [Publications of First Psychiatric Hospital of Moscow. Part 2. Jubilee Number, One Hundred and Thirty Years.] Cloth. Price, 12 rubles. Pp. 416, with illustrations. Moscow, 1939.

Trudy I-oy Moskovskoy Psikhiatricheskoy Bolnitsy. Vypusk tretiy. Pod obshchey redaktsiey: M. A. Dzhagarova. [Publications of First Psychiatric Hospital of Moscow. Part 3.] Cloth. Price, 20 rubles. Pp. 488, with illustrations. Moscow, 1940.

Volume II of the reports of the First Psychiatric Hospital of Moscow presents a number of papers dealing with the effects of convulsion therapy. Volume III is devoted to a follow-up study of 607 schizophrenic patients treated in the past four years by the various active methods (convulsion therapy).

Tuberkulez u detey. Pod redaktsiey i s predisloviem: N. M. Frishmana. [Tuberculosis in Children.] Cloth. Price, 23 rubles. Pp. 370. Kharkov: Izdanie I-go Kharkovskogo Meditsinskogo Instituta, 1940.

Tuberculosis in children is a collection of papers by the members of the pediatric faculty of the Kharkov Medical Institute edited by Prof. N. M. Frishman. The papers deal with the clinical aspects of the various forms of tuberculosis seen in children. No new or original points of view are presented.

Rheumatism: Notes on Its Causes, Its Incidence and Its Prevention; with a Plan for National Action. By Lord Horder (in Collaboration with the Empire Rheumatism Council). Paper. Price, 2s. Pp. 60. London: H. K. Lewis & Co., Ltd., [n. d.].

In this small booklet, Lord Horder discusses rheumatic disorders from the point of view of incidence and causes, and available therapeutic measures. He proposes a national scheme of treatment and discusses the problem of finance and, in an appendix, rheumatism in the defense services. Quite naturally, the treatment of each of these subjects is brief.

O travmaticheskikh aneyrizmakh yagodichnykh arteriy. [By] P. L. Shupik. S predisloviem V. N. Shamova. [Traumatic Aneurysm of Gluteal Arteries.] Paper. Price, 3 rubles. Pp. 55, with illustrations. Kharkov: Izdanie I-go Kharkovskogo Medinstituta, 1939.

This brief monograph deals with a rare lesion, traumatic aneurysm of the gluteal arteries. The author reports two cases and reviews the literature. The therapy indicated is early operative intervention preceded by intraperitoneal ligation of the hypogastric artery and involving resection of the aneurysmal sac and ligation of all bleeding vessels. The best approach is obtained by sectioning the insertion of the gluteus maximus muscle.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

NYLON HOSIERY AND PERSPIRATION

To the Editor:—Can you tell me anything about the chemical composition of Nylon hosiery? A patient tells me that she had a large swelling on the side of the leg which the local physician told her was due to vitamin B deficiency and that Nylon hosiery is so constructed that it does not absorb perspiration. On questioning her further, she said that a friend of hers had a story of chilblains of her feet and aching of her legs. She went into her husband's office one day and said to the secretary "I can hardly wait to sit down and take off my shoes." The secretary asked her if, by chance, she wore Nylon stockings. She said she did. The secretary said that she had worn Nylon stockings and found that she had aching of the legs and feet. A doctor whom she consulted said "I think your trouble may be that you are wearing Nylon hosiery, which does not absorb the perspiration. Stop wearing them." The secretary did this and the trouble cleared up. My patient too has stopped wearing Nylon hose along with taking vitamin B, and her trouble is clearing. I should like to find out whether the chemical composition of Nylon hose is such that this substance does not absorb perspiration as well as silk or cotton and whether the latter fabrics better promote the distribution of perspiration and circulation of the skin. Is there evidence that people are having pains in the legs from wearing this type of hosiery? It seems to me that if this condition exists the public should be prevented from wasting money and getting into the foot trouble class. Merrill Moore, M.D., Boston.

ANSWER.—Nylon is the trade name for a synthetic resin which is a polymer of hexamethylenediamine adipate. Patch tests performed with this substance prove that it is not a primary cutaneous irritant. This, in common with other water insoluble resins, does not absorb perspiration, but this fact would not account for the foot trouble described.

Perspiration on the legs covered with stockings evaporates through the mesh of the stockings before there is any chance for the fiber to absorb it even if the fiber is absorptive. Though silk fiber will absorb perspiration, little of it is absorbed by that part of the stocking covering the legs because of the fact that it evaporates through the mesh. One of the principal reasons why Nylon stockings have achieved popularity is the fact that they are more "sheer" than silk stockings. This means that there is more open space in Nylon stockings than in similar silk stockings, and perspiration can evaporate more rapidly.

There is no evidence to show that there are differences in the circulation of the blood through the skin when one is wearing silk, cotton or Nylon stockings. There have been no reports in literature of people having pains in the legs caused by wearing Nylon hosiery. There have been reports of dermatitis occurring among people wearing Nylon hosiery, but it has been proved that this dermatitis was not caused by the Nylon but by a finish used on the Nylon by certain factories, and this same finish caused dermatitis when used on silk stockings, cotton shorts and other wearing apparel. There was a wave of dermatitis throughout Canada and the United States caused principally by this new synthetic resin finish which was reported in THE JOURNAL, Sept. 14, 1940, page 906, under the title of "An Outbreak of Dermatitis from New Resin Fabric Finishes," by Schwartz and others.

It is true that the part of the foot which is covered by a shoe such as men wear may become more moistened with perspiration when Nylon or other fabric made of resins is worn than when a natural fabric, such as silk, cotton or wool, is worn; but evaporation from open type shoes worn by women and absorption by the backing in the shoes (usually made of cotton) keep the feet encased in Nylon stockings from becoming excessively wet from perspiration.

STERILIZATION OF SULFATHIAZOLE POWDER

To the Editor:—I read your answer to the question of the mode of sterilization of sulfonilamide powder. You mentioned the safety of autoclaving the drug. Does the same hold true for sulfathiazole powder? Is it necessary to sterilize sulfathiazole for local use? If so, is it safe to autoclave the powder or is the use of dry heat preferable? Sidney Kahn, M.D., New York.

ANSWER.—It is possible to sterilize sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine by heating at 140 C. for four hours. It is also possible to autoclave small amounts of the drugs in flasks at 15 pounds pressure for twenty minutes. This will sterilize the powder, but occasionally there is a tendency for the powder which has been sterilized in this fashion to cake in the flask.

EFFECT OF BARIUM CARBONATE FUMES ON RESPIRATORY TRACT

To the Editor:—Several patients employed in a factory where bombs are heated in barium carbonate melted with electrodes in a tank complained of a persistent cough. This molten barium carbonate gives off fumes, and there is no special ventilating device to combat these fumes. Are these fumes responsible for the bronchial irritation. M.D., Wisconsin.

ANSWER.—In the situation described there are several imponderables that prevent a clearcut answer. In the molten state the temperature of this chemical mass probably exceeds 1,700 C., at which temperature and even lower barium carbonate decomposes into barium oxide and carbon dioxide. In the form of fume, the barium oxide in the atmosphere partly returns to the carbonate state. Likewise the molten material probably represents a mixture of barium oxide and carbonate. The barium ion always is toxic when absorbed and the complete nontoxicity of barium sulfate, as when used for opaquing purposes in roentgen ray work, is chiefly due to its insolubility. Barium carbonate is likewise largely insoluble in water, but fatalities have arisen through the accidental substitution of this material for barium sulfate. Granting that the fumes represent barium oxide, a caustic action akin to that of calcium oxide or unslaked lime is possible. However, in steel carbonization large quantities of barium carbonate along with charcoal may be utilized under conditions of dustiness far in excess of ordinary fumes from a molten barium carbonate bath. Yet bronchitis from this source is not common. Under electrolytic action, the simple decomposition of barium carbonate described possibly may be modified so that other and more active barium compounds may be evolved. In this situation there is the possibility that nascent oxygen may be evolved, which form of oxygen constitutes a respiratory irritant.

In the query it is not mentioned that the bomb casings are coated with oil. Should this be true, the heat decomposition of oil might lead to respiratory irritants.

Kipper (*München. med. Wchnschr.* **73**:2180, 1926) describes a fatal industrial barium poisoning from a mixture of the oxide and the carbonate. In this instance the exposure was to dust. This author's animal experiments led to the belief that the carbonate may be absorbed from the lungs. In this case there appeared gastric pain, vomiting, dyspnea, muscular paralyses, rapid heart rate and increased blood pressure. McNally (Toxicology, Chicago, Industrial Medicine, 1937) likewise mentions conjunctivitis and nasal and respiratory tract inflammation as a result of barium poisoning, associated with diarrhea. In severe poisoning the blood coagulation time is increased, tests for which may be of value. Any barium carbonate reaching the stomach may be changed by gastric hydrochloric acid into the chloride, which barium salt is readily soluble and highly toxic.

In this industrial operation there should be good ventilation to avoid more than traces of any barium compound in the atmosphere breathed by workmen.

IMPAIRED PERIPHERAL CIRCULATION IN GIRL

To the Editor:—An otherwise perfectly healthy girl of 16 has suffered all her life from poor circulation in the hands and feet, more particularly in the hands, which are purple at all times and show evidences of sluggish circulation. Practically every kind of therapy has been tried at various times without any success except a possible improvement from the use of electrical treatments. Can you suggest the causation and therapy? A year ago she had two attacks of severe migraine, which has not returned since she was found to be allergic to corn and this food has been avoided. M.D., Ottawa, Ont.

ANSWER.—Before a definite diagnosis can be made it is necessary to know the state of the pulsations of the peripheral arteries and to determine whether or not there is an organic basis for the impaired circulation. It is also important to exclude causes to which the impaired circulation could be secondary, such as involvement of the nervous system. Presuming that this patient does not have an organic disease to which the disturbed circulation could be secondary and presuming that she does not have organic occlusion of her arteries, it is probable that the circulation is on the basis of persistent arteriolar spasm with capillary dilatation. This situation usually accounts for "poor circulation," characterized by persistent coldness and cyanosis of the skin. The condition may be characterized as erythrocyanosis or acrocyanosis, or as livedo reticularis. Cervicothoracic sympathectomy may relieve this condition in the hands and lumbar sympathectomy in the feet. However, before these operations are carried out it is advisable to perform tests to determine the degree of probability that such operations will give relief. To this end, release of arteriolar spasm could be accomplished by injection of the appropriate

sympathetic nerves with procaine hydrochloride, by subjecting the patient to an environmental temperature of about 86 F., or by inducing fever artificially by the intravenous injection of typhoid vaccine. If these methods produce improvement in the color and in the warmth of the skin, sympathectomy is a logical procedure.

FUNCTIONAL UTERINE HEMORRHAGE

To the Editor:—A girl aged 17 years who had had fairly regular menses began to bleed from the uterus. She was sent to a hospital and was treated with ergot preparations, antuitrin S and radium, and as a last resort curettement was performed. Curettement revealed a soft, spongy endometrium. There was little improvement. The patient continued to bleed for weeks but finally stopped. Two weeks ago she began to bleed in the same way. Can you suggest a diagnosis or treatment? She does not exhibit any symptoms of menopause except the bleeding.

H. K. Owens, M.D., Elkins, W. Va.

ANSWER.—It was unfortunate that the "soft spongy endometrium" which was obtained with the curet was not subjected to microscopic examination. Before therapy is instituted it is important to try to make a diagnosis. In spite of the long history and the patient's age, another curettement should be performed to rule out cancer. If carcinoma is present the patient must be treated according to the accepted methods of dealing with carcinoma of the uterus, which consists of both operation and radiation therapy. Most likely the patient has a functional menorrhagia. The soft, spongy endometrium may indicate the presence of hyperplasia. Microscopic examination of the endometrium will reveal the true condition of the endometrium. If the bleeding is of benign origin, it may be stopped by administration of 25 mg. of testosterone propionate intramuscularly three times a week for four or six weeks. When more than 300 mg. of testosterone propionate is given, there is some likelihood that symptoms of virilism may appear. These are growth of hair on the face, a lowered pitch of the voice and slight enlargement of the clitoris. However, these signs disappear after the medication is stopped, and, in view of the patient's persistent bleeding, this form of therapy may be tried. After the bleeding has been checked it is advisable to give the patient 25 mg. of testosterone propionate each week for a few weeks as a prophylactic.

PERIPHERAL NEURITIS OR PERNICIOUS ANEMIA

To the Editor:—A white woman aged 42 complains of pain along the distribution of the left sciatic nerve and the right ulnar and median nerves. She has been sick for one year with pains all over her body, at times in one arm, at times in the intercostal spaces. The pain has followed the course of practically all the nerves. Associated with pain there is tenderness along the course of nerves and a sensation of numbness. She has been subjected to the following examinations with negative results: roentgenoscopy of sinuses and teeth, chest, gallbladder, gastrointestinal tract and the lumbar spine; basal metabolism; dextrose tolerance; examination of feces; complete blood and urine examination, including uric acid and nonprotein nitrogen; physical examination, which was entirely negative except for tenderness over the nerve which happened to be affected at the time of the examination. All reflexes have been within normal limits. At present she is getting (1) about one hour of diathermy to the left hip and right shoulder every other day; (2) 50 mg. of thiamine hydrochloride every other day hypodermically; (3) 6 mg. of thiamine hydrochloride four times daily by mouth; (4) foreign protein in the form of milk every other day; (5) two capsules of thiamine hydrochloride three times a day. Do you think the diagnosis of peripheral neuritis is correct? Do you think the dosage of thiamine hydrochloride is sufficient? Would you suggest further diagnostic procedure or treatment? Within the past two weeks, since she has been on this regimen, she has been a little improved for the first time within a year.

M.D., Kentucky.

ANSWER.—From the information submitted one cannot make a diagnosis. The subjective symptoms suggest an avitaminotic deficiency or pernicious anemia with spinal cord involvement.

The following are recommended: a complete neurologic examination to determine the presence of objective evidence of organic disease of the central and peripheral nervous system and a gastric test meal to determine the presence or absence of free hydrochloric acid. In 30 per cent of the cases of pernicious anemia the spinal cord signs and symptoms antedate for months or for several years the blood picture of pernicious anemia.

From the findings given a diagnosis of peripheral neuritis cannot be made.

If thiamine hydrochloride is given it should be administered hypodermically in doses of 100 to 150 mg. daily.

If the patient has pernicious anemia, large doses of liver extract should be given intramuscularly at least three times weekly. Each injection of liver should be equivalent to 6 pounds of whole liver. In addition, the patient should eat liver. The liver therapy is continued until those symptoms of pain and numbness disappear.

TONGUE SWALLOWING AS CAUSE OF DEATH

To the Editor:—A careful search in the standard works on legal medicine has failed to reveal an answer to the question does death by asphyxiation by means of choking due to obstruction of the pharynx from a falling backward of a relaxed tongue in persons under deep anesthesia occur? It is assumed that such a person would have been left unattended, without an airway in the mouth and flat on his back. I have had a fair amount of experience in necropsy work but so far have never encountered such a case. Recently death was thought to be due to such a cause but a complete postmortem examination failed to disclose any obvious cause of death other than a mild degree of chronic passive hyperemia of the lungs. One of the barbiturate anesthetics was used intravenously, and anesthesia was not unusually deep. Death may have been due to postoperative shock, since reamputation of an infected stump of the right leg had been done. I will appreciate any opinion which may be offered as regards choking by "swallowing the tongue" or any pertinent references to the literature.

Lawrence Parsons, M.D., Reno, Nev.

ANSWER.—The occurrence of so-called tongue swallowing is thought to result from the loss of tone of the muscles of the lower jaw in deep anesthesia. The jaw with its structures falling back allows the base of the tongue to lie against the posterior wall of the pharynx, causing partial or complete obstruction to respiration. The phenomenon may be considered a part of the general muscular relaxation and is difficult or impossible to determine at necropsy. In a study of a large number of anesthesia deaths which were examined post mortem there was no instance of death due to tongue swallowing and a search of the literature fails to reveal an authentic case, although in all probability death has occurred from the phenomenon.

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FLAKE NAPHTHALENE AND AURAL SYMPTOMS

To the Editor:—A man aged 38, in good health, began a job about five months ago where he is constantly exposed to fumes from naphthalene flakes in packing clothing. About three weeks after starting this job he began to have a hissing, escaping sound in his ears. His hearing is normal. Have you any data to support the theory that naphthalene fumes are responsible? If so, what would you suggest doing in treatment?

M. P. Weems, M.D., Jeffersonville, Ind.

ANSWER.—Flake naphthalene, used as a moth repellent on woolen garments and other fabrics, has been so extensively applied for several decades that any characteristic injurious properties long since would have become apparent. In its manufacture and in its use as an intermediate in the preparation of naphthols and naphthylamines, naphthalene fume may lead to a veritable snowstorm effect in the atmosphere. Apart from occasional eczematoid dermatitis, corneal and conjunctival irritation, nausea and vomiting this substance has attracted scant attention as an injurious agent. These manifestations chiefly have been limited to the manipulation of naphthalene in the molten or hot state, or at least in high concentrations. Anhydrosis, a feeling of excessive warmth of the skin, skin edema, chorioretinitis and optic neuritis have been reported. In a few instances red blood cells have been found in the urine, which has been associated with mild anemia. Any connection between the described aural condition and naphthalene is doubtful. Causal relationship perhaps should be denied unless further examinations disclose evidences of ocular injury, aural edema, hematuria and anemia not otherwise accounted for. The presence of a chemical dermatitis of unknown origin further would support the possibility of naphthalene injury. In general, flake naphthalene present in connection with the packing of clothing must be regarded as a substance of low toxicity.

CONGENITAL BILATERAL PTOSIS

To the Editor:—In congenital bilateral ptosis, at what age should surgery be attempted and which operation is generally considered best suited for this type?

B. M. Wilson, M.D., Alexandria, La.

ANSWER.—There are several phases to be considered in answering this question. If the ptosis is so advanced that the pupillary area of the cornea is covered, surgical correction should be performed as early as possible, from 1 to 2 years of age. But if the vision is not impaired by the drooping lid, it is preferable to postpone the operation until the age of 6 or 8 years.

The second if deals with the absence or presence of fixation of the levator muscle. As a rule, in congenital types there is enough action present to make the Blaskovicz the most suitable type of operation; however, if no action of the levator can be demonstrated, some form of transplantation of a tongue of the superior rectus muscle is preferable.